UNIVERSIDADE DE BRASÍLIA
FACULDADE DE CEILÂNDIA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS E TECNOLOGIAS EM SAÚDE

ELETROESTIMULAÇÃO NEUROMUSCULAR COMO ESTRATÉGICA PRECOCE PARA PRESERVAR A MUSCULATURA PERIFÉRICA EM INDIVÍDUOS POLITRAUMATIZADOS SOB VENTILAÇÃO MECÂNICA

Luciana Vieira Tavernard de Oliveira Urache

BRASÍLIA
2016

LUCIANA VIEIRA TAVERNARD DE OLIVEIRA URACHE

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Tese de Doutorado apresentada à Faculdade de Ceilândia da Universidade de Brasília como requisito parcial à obtenção do título de Doutor em Ciências e Tecnologias em Saúde.

Área de Concentração: Promoção, Prevenção e Intervenção em Saúde

Linha de Pesquisa: Saúde, Funcionalidade, Ocupação e Trabalho

Orientador: Prof. Dr. Gerson Cipriano Junior

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“I still fall on my face sometimes
And I can't color inside the lines
Cause I'm perfectly incomplete
I'm still working on my masterpiece

And I, I wanna hang with the greatest
Got a way to go, but it's worth the wait
No, you haven't seen the best of me
I'm still working on my masterpiece...”

Josh Alexander

Ao João Gabriel, que trouxe luz e som às nossas vidas!...

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Quatro anos. A gente costuma dizer que passa voando. Eu, como boa doutoranda, vou me permitir polemizar e discordar do senso comum, e dizer que demora muito. Muito mesmo. Uma eternidade... Dá tempo de sonhar com um projeto, cair na real, sonhar de novo. Adoecer subitamente, passar por uma cirurgia de emergência e uma temporada na UTI, se recuperar. Engravidar, perder o bebê aos cinco meses de gestação, sobreviver. Apresentar resultados preliminares em um, dois, três, quatro congressos internacionais. Pedir exoneração pela quinta vez. Estudar e viver um ano em outro país. Testemunhar seus filhos aprendendo a ler, escrever e questionar. Gestar um *paper*, depois outro, mais um, e começar a entender que um manuscrito é um processo, e não um produto... Prometer a si mesma e aos que te amam que nunca mais fará isso de novo. Perceber que em breve essa promessa será desfeita... Tornar-se referência em algo para alguém. E, ao final, compreender que apenas aumentou o conhecimento de tudo que você ainda não sabe...

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RELAÇÃO DE SIGLAS, SÍMBOLOS E ABREVIATURAS

AU	unidades arbitrárias
CNPq	Conselho Nacional de Desenvolvimento Cientifico e Tecnológico
CONSORT	Consolidated Standards of Reporting Trials
EENM	estimulação elétrica neuromuscular
FEPECS	Fundação de Ensino e Pesquisa em Ciências da Saúde
ICC	coeficiente de correlação intraclasse
IGF-I	insulin-like growth factor I
IFN-y	
IRS-I	substrato do receptor de insulina I
MMP	metaloproteinase de matriz
PDSE	Programa de Doutorado Sanduíche no Exterior
REBEC	Registro Brasileiro de Ensaios Clínicos
SES/DF	Secretaria de Saúde do Distrito Federal
TCLE	Termo de Consentimento Livre e Esclarecido
TNF α	Fator de Necrose Tumoral Alfa
UTI	Unidade de Terapia Intensiva
VM	ventilação mecânica

RESUMO

Introdução: A segurança e reprodutibilidade da ultrassonografia para avaliação da musculatura esquelética em indivíduos politraumatizados criticamente enfermos ainda não foram avaliados. Politraumatizados são geralmente jovens e previamente saudáveis, mas estão expostos à inflamação e inatividade desde o momento pré-hospitalar, o que pode levar a uma deterioração muscular precoce e mais grave. A estimulação elétrica neuromuscular (EENM) pode ser benéfica a esses pacientes.

Objetivos: (i) Avaliar a segurança e reprodutibilidade da avaliação muscular por ultrassonografia; (ii) descrever mudanças precoces na espessura e ecointensidade muscular, e mediadores de sinalização de crescimento muscular e inflamação sistêmica; (iii) avaliar a efetividade de um protocolo precoce e de curto prazo de EENM para minimizar o dano muscular.

Métodos: (i) Estudo de segurança e reprodutibilidade da aquisição e análise das imagens do musculo quadríceps por dois examinadores, com e sem experiência prévia em ultrassonografia; (ii) estudo prospectivo observacional; para avaliar o dano muscular, foram obtidos por cinco dias consecutivos medidas sonográficas de ecointensidade e espessura muscular, e níveis séricos de insulin-like growth factor I (IGF-I) e citocinas inflamatórias; (iii) ensaio clínico randomizado; o grupo intervenção recebeu uma sessão diária de EENM bilateral no quadríceps, por cinco dias consecutivos, enquanto o grupo controle recebeu apenas o tratamento convencional; a espessura e ecointensidade muscular foram avaliadas por ultrassonografia; mediadores de sinalização do crescimento muscular – IGF-I and metaloproteinase de matriz (MMP)-2, e inflamação – citocinas e MMP-9, foram quantificados em amostras sanguíneas.

Resultados: (i) Excelente reprodutibilidade foi encontrada tanto para aquisição quanto para a análise das imagens; os valores de ecointensidade medidos pelo método do quadrado foram maiores do que pelo traçado; (ii) ao longo de cinco dias, observou-se um aumento na ecointensidade e uma redução na espessura musculares; os níveis séricos de IGF-I diminuíram, assim como a IL-4, enquanto as

citocinas pró-inflamatórias aumentaram; (iii) o grupo EENM teve ecointensidade e espessura melhor preservadas em comparação ao grupo controle, com menor redução nos níveis séricos de IGF-I e MMP-2, maior aumento nos níveis de IL-4, menor aumento no IFN-y, redução no TNF-α e na MMP-9.

Conclusão: A ultrassonografia é um método seguro e reprodutível para avaliação muscular em indivíduos politraumatizados criticamente enfermos, independente do nível de experiência do examinador. Mudanças significativas na espessura e ecointensidade muscular iniciam-se já em 48 horas após a admissão hospitalar, com redução no IGF-I e alterações nas citocinas. A EENM é uma estratégia efetiva para prevenir o dano muscular nesses indivíduos.

Palavras-chave: Eletroestimulação. Politrauma. Ventilação mecânica. Ultrassonografia. Dano muscular. Mobilização precoce.

ABSTRACT

Rationale: Ultrasound safety and reliability in critically ill trauma patients is still unclear. Major trauma patients are usually young and previously healthy, but are exposed to inflammation and inactivity since pre-hospital phase, which may lead to an earlier and worsen impairment. Neuromuscular electrical stimulation (NMES) may benefit those patients.

Objectives: (i) To assess the safety and reliability of ultrasound muscle assessment; (ii) to describe the very early changes in muscle quality and size, and signaling mediators of muscle growth and systemic inflammation; (iii) to investigate the efectiveness of an early and short-term protocol of NMES to alleviate acute muscle wasting in critically ill trauma patients.

Methods: (i) Study of safety and reliability of image acquisition and analysis by two examiners, with and without previous expertise in ultrasonography; (ii) prospective observational study; to examine skeletal muscle wasting, serial ultrasound measures of muscle echogenicity and thickness, and circulating levels of insulin-like growth factor I (IGF-I) and inflammatory cytokines, were obtained for five consecutive days; (iii) randomized controlled trial; intervention group received a daily session of bilateral NMES on quadriceps muscle, for five consecutive days, while control group received usual care alone; muscle echogenicity and thickness were daily evaluated by ultrasonography; signaling mediators of muscle growth – IGF-I and matrix metalloproteinase (MMP)-2, and inflammation – cytokines and MMP-9, were assessed in blood samples.

Results: (i) Excellent reliability was found both for image acquisition and analysis; echogenicity values were higher using the square versus the trace technique; (ii) an increase on echogenicity and a decrease on thickness were observed over the five days; circulating levels of IGF-I decreased, as well as IL-4, while pro-inflammatory cytokines increased; (iii) NMES group had better-preserved muscle echogenicity and thickness compared to control, with a smaller decrease in IGF-I and MMP-2, a greater increase in IL-4, a smaller increase in IFN-y, a decrease in TNF- α and a decrease in MMP-9.

Conclusions: Ultrasound is safe and reliable for muscle assessment in critically ill trauma patients, regardless of the assessor's level of expertise. Significant changes on muscle quality and size start as early as 48 hours after hospital admission, with decrease in IGF-I and change in cytokines levels. NMES is an effective strategy to prevent muscle wasting in those patients.

Key Words: Electrical stimulation. Polytrauma. Mechanical ventilation. Ultrasonography. Muscle damage. Early Mobilization.

1 INTRODUÇÃO GERAL

A presente tese foi redigida na modalidade de artigos científicos, em uma abordagem de artigos verticais ou sequenciais, de acordo com as Normas para Preparo da Dissertação ou da Tese para Obtenção do Título de Mestre ou de Doutor do Programa de Pós-Graduação em Ciências e Tecnologias em Saúde da Universidade de Brasília, sendo composta pelos seguintes elementos:

- Introdução geral, com contextualização e apresentação da contribuição do estudo à literatura científica, justificativa e os objetivos propostos;
- Três artigos científicos, apresentados conforme as normas específicas dos periódicos para os quais foram submetidos;
- Discussão geral e conclusões;
- Como apêndice, constam o Termo de Consentimento Livre e Esclarecido (TCLE); uma relação com as contribuições científicas ao longo do período de Doutorado; e um relatório das atividades realizadas durante o Programa de Doutorado Sanduíche no Exterior (PDSE);
- Em anexo, estão apresentados o Parecer Consubstanciado do Comitê de Ética em Pesquisa da FEPECS/SES-DF (Fundação de Ensino e Pesquisa em Ciências da Saúde/Secretaria de Saúde do Distrito Federal); o Registro Brasileiro de Ensaios Clínicos (REBEC); as normas de publicação dos periódicos aos quais foram submetidos os artigos científicos, o Qualis dos periódicos e os comprovantes de submissão.

1.1 CONTEXTUALIZAÇÃO

O politrauma é a maior causa de morte e incapacidade em adultos jovens previamente hígidos, sem déficits musculoesqueléticos prévios e clinicamente saudáveis, no Brasil (1) e no mundo (2, 3). O traumatismo grave está associado a uma taxa de mortalidade de 30% a 70%, e a recuperação dos sobreviventes é marcada por déficits funcionais significativos, que perduram após a alta hospitalar (4-6).

Tais déficits se agravam devido ao tempo prolongado de internação hospitalar após o trauma, em geral acompanhado de imobilidade, sepse, síndrome da resposta inflamatória sistêmica, disfunção orgânica múltipla, hiperglicemia, uso prolongado de ventilação mecânica, e uso de corticosteroides, bloqueadores neuromusculares e/ou antibióticos (7). Esses fatores em conjunto levam a disfunções neuromusculares, sendo a mais comum a polineuropatia do paciente critico (8), que atinge tanto a musculatura respiratória quanto a periférica (9), e leva a redução de trofismo (10) e força muscular (11).

A fraqueza muscular adquirida afeta grande parte dos pacientes críticos (12). Entre os indivíduos com síndrome do desconforto respiratório agudo, 60% desenvolvem polineuropatia (13). Na sepse ou síndrome da resposta inflamatória sistêmica, a incidência sobe para 70% (14), podendo atingir 100% dos indivíduos com disfunção orgânica múltipla (15). Em populações não específicas com quatro a sete dias de ventilação mecânica (VM), a incidência varia de 25-33% (diagnóstico por avaliação clínica) (14, 16, 17) a 58% (diagnóstico por avaliação eletrofisiológica ou biópsia) (18, 19). A partir de sete dias de VM, mesmo apenas com diagnóstico clínico, a incidência sobe para 49-77% (20, 21).

A debilidade muscular do paciente crítico está associada a alterações da estrutura da fibra muscular, com perda de filamentos de miosina e aumento de enzimas proteolíticas, mesmo em indivíduos que não receberam altas doses de esteroides ou bloqueadores neuromusculares (22). Longos períodos em VM também apresentam associação com importantes alterações nas fibras musculares e marcadores inflamatórios (23).

A musculatura esquelética é regulada por um balanço entre a síntese e degradação muscular proteica (24). Em indivíduos criticamente enfermos, a alteração das vias metabólicas e inflamatórias leva a uma deterioração da função muscular (25). A síntese muscular também está precocemente alterada em doentes críticos (25), como demonstrado pela menor expressão de substâncias envolvidas na via anabólica muscular, como o substrato do receptor de insulina I (IRS-I) (26).

A combinação de inflamação precoce e inatividade nos indivíduos politraumatizados pode ter um efeito deletério direto e profundo no dano muscular, afetando tanto as vias de síntese quanto de degradação proteica; a inatividade em

doentes críticos permite uma exposição prolongada a citocinas miócito-degradantes e promove um desequilíbrio nas citocinas, levando a uma degradação pró-inflamatória dos miócitos (27). Por sua vez, o trauma promove uma resposta inflamatória aguda por meio da liberação de citocinas pró-inflamatórias (28); as citocinas estão alteradas desde a Unidade de Emergência, persistindo nos dias subsequentes e perpetuando o estado inflamatório (29). Mesmo em indivíduos jovens saudáveis sob imobilização gessada, há uma resposta de sinalização muscular divergente no que se refere à expressão de mioestatina e aos componentes do sistema ubiquitina-proteossoma, demonstrada por imuno-histoquímica (30).

O fator de crescimento semelhante à insulina tipo I (*insulin-like growth factor I* – IGF-I) é uma proteína sintetizada no fígado em resposta ao Hormônio do Crescimento, com papel importante no desenvolvimento muscular (31). O IGF-I ativa vias de sinalização responsáveis por regular a síntese proteica e induzir a hipertrofia da musculatura esquelética (32), e é o principal sinalizador da via de ativação de translação proteica, sendo estimulado durante a carga mecânica do músculo (33); em estados catabólicos, a redução na secreção de IGF-I reduz a síntese proteica e/ou estimula a degradação proteica, piorando a atrofia muscular (34). A ausência de mecanossinalização decorrente da inatividade foi apontada recentemente como um fator de disparo da miopatia do paciente crítico (33). Munoz-Canoves e colaboradores (35) propuseram em estudos em animais que, em decorrência da inatividade e da inflamação, níveis elevados de interleucina (IL) 6 promovem atrofia muscular por meio de efeitos indiretos na via de sinalização do IGF-I, comprometendo a via anabólica de síntese muscular (25). Esse é o primeiro estudo que mensura o IGF-I em indivíduos criticamente enfermos.

As metaloproteinases de matriz (MMP) desempenham um importante papel homeostático na matriz extracelular durante os processos de crescimento e reparo muscular (36), e podem ser biomarcadores valorosos para refletir o impacto da atividade no estado inflamatório (37). A MMP-2 regula a integridade e composição da matriz extracelular na musculatura esquelética, sendo fundamental para a proliferação, diferenciação, e regeneração das fibras musculares após injúria, e na manutenção do tecido conectivo circunjacente (38); em um modelo de transsecção do ligamento cruzado anterior em ratos, a EENM regulou os níveis de MMP-2, sugerindo adaptações benéficas no quadríceps após a estimulação elétrica (39). A MMP-9 está

envolvida na degradação da matriz extracelular, e é pró-inflamatória (40); baixos níveis de concentração plasmática nas primeiras 48 horas após injúria foram preditivos de menor tempo de permanência na Unidade de Terapia Intensiva (UTI) e menor taxa de mortalidade após traumatismo grave (41).

A debilidade muscular tem forte impacto no prognóstico dos indivíduos internados em UTI (26, 42, 43), estando associada a internação prolongada, dificuldade no desmame da ventilação mecânica, maior mortalidade e aumento dos custos intra e extra hospitalares (44-46). Mesmo após um ano de alta hospitalar, o status funcional de pacientes que permaneceram mais de dois dias internados em UTI permanece alterado em 54% dos indivíduos (13, 47) o que corrobora a necessidade de intervenções precoces e efetivas nesses indivíduos.

Até o momento, oito revisões sistemáticas confirmam o benefício da mobilização em indivíduos criticamente enfermos (6, 48-54); a reabilitação precoce é segura e factível (6, 48) e resulta em melhoria na qualidade de vida (49), função física (49, 50), e força muscular periférica e respiratória (49, 51); melhor prognóstico funcional pós-alta (6), como independência funcional (51) ou mais indivíduos caminhando sem assistência no momento da alta hospitalar (52); maior número de dias livres de ventilação mecânica (49, 51, 53), menor tempo de permanência na UTI e no hospital (49, 51, 54), e subsequente redução nos custos de hospitalização (54).

No entanto, há um crescente interesse quanto ao uso da tecnologia assistiva para minimizar os danos funcionais inerentes à permanência em unidades de cuidados intensivos (23, 55), principalmente nas fases iniciais, quando o indivíduo ainda não é capaz de cooperar com programas de mobilização ativa (53, 56, 57). A estimulação elétrica neuromuscular (EENM) permite uma contração passiva da musculatura esquelética, por meio da utilização de impulsos elétricos aplicados através da pele para a musculatura a partir de eletrodos de superfície. Ela não depende da cooperação do paciente, podendo ser iniciada de forma precoce, mesmo em pacientes sedados (23), e vem emergindo como uma estratégia segura, de baixo custo e ampla aplicabilidade em pacientes críticos. A EENM mimetiza os efeitos de contrações musculares repetitivas durante o exercício, com melhora no fluxo sanguíneo intramuscular, produção de força muscular máxima e endurance muscular em indivíduos com redução de força muscular no quadríceps (58, 59).

A implementação da EENM produz melhora significativa na força muscular e capacidade de exercício em indivíduos com doença pulmonar obstrutiva crônica e insuficiência cardíaca (60). Estudos recentes tem observado preservação da massa muscular (10), melhora da força periférica global e redução do tempo de desmame com o uso de EENM em indivíduos criticamente enfermos (61). Os mecanismos de alteração aguda da função muscular e de ação da EENM em indivíduos politraumatizados criticamente enfermos ainda não foram elucidados.

1.2 HIPÓTESE

A hipótese principal deste estudo é que indivíduos politraumatizados criticamente enfermos desenvolvem dano muscular periférico já na primeira semana após admissão na Unidade de Emergência. Tal dano tem impacto na estrutura muscular, traduzida em redução da espessura e aumento da ecointensidade muscular, avaliada de forma não invasiva por meio de ultrassonografia. Os mecanismos envolvidos no dano ou preservação da musculatura estão relacionados à síntese ou degradação proteica; hipotetizamos que, em função do imobilismo e inflamação precoce e intenso secundários ao politrauma, as vias de sinalização de hipertrofia muscular por meio do IGF-I estaria inibida, e haveria um desequilíbrio nas citocinas inflamatórias. Como estratégia de tratamento, hipotetizamos que um programa de eletroestimulação neuromuscular precoce e de curto prazo seria capaz de minimizar tal dano, preservando a espessura e ecointensidade muscular por meio de menor redução nas vias de sinalização de síntese muscular – IGF-I and MMP-2 – e de uma regulação da inflamação sistêmica, por meio de um melhor equilíbrio das citocinas pró- (IL-2, IL-6, TNF-α, e IFN-y) e anti-inflamatórias (IL-4, e IL-10) e da MMP-9.

Para testar as hipóteses, foram realizados três estudos, como se segue:

- Estudo 1: *Reliability of skeletal muscle ultrasound in critically ill trauma patients;*
- Estudo 2: *Acute skeletal muscle wasting assessed with ultrasound and mediators of muscle growth and systemic inflammation in critically ill trauma patients: a prospective observational study;*

- Estudo 3: *Neuromuscular Electrical Stimulation Alleviates Muscle Wasting in Critically Ill Trauma Patients.*

1.3 OBJETIVOS

Objetivo Geral

Identificar o dano muscular periférico precoce após admissão hospitalar em indivíduos politraumatizados criticamente enfermos, por meio da avaliação da estrutura muscular – espessura e ecointensidade – por ultrassonografia; e do comportamento de marcadores inflamatórios – citocinas pró e anti-inflamatórias – e de sinalização da via anabólica de síntese muscular – IGF-I – na corrente sanguínea; avaliar o efeito da inclusão de um protocolo de eletroestimulação junto ao tratamento convencional (fisioterapia respiratória, mobilização passiva e posicionamento) na musculatura periférica desses indivíduos, por meio da avaliação da estrutura muscular – espessura e ecointensidade – por ultrassonografia; e do comportamento de marcadores inflamatórios – citocinas pró e anti-inflamatórias e MMP-2 – e de sinalização da via anabólica de síntese muscular – IGF-I e MMP-9 – na corrente sanguínea.

Objetivos Específicos

- Objetivo 1: avaliar a segurança e viabilidade da avaliação muscular do quadríceps por ultrassonografia no Unidade de Emergência; avaliar a reprodutibilidade intra e inter-examinador entre profissionais de saúde com diferentes níveis de experiência prévia, para a aquisição e análise de imagens sonográficas de espessura e ecointensidade muscular em indivíduos politraumatizados criticamente enfermos;
- Objetivo 2: caracterizar a variação da espessura e ecointensidade muscular, bem como os níveis séricos de IGF-I e citocinas pró e anti-inflamatórias, ao longo de cinco dias consecutivos após a admissão hospitalar; analisar a relação entre parâmetros sonográficos musculares e mediadores de

sinalização de síntese muscular e inflamação sistêmica em indivíduos politraumatizados criticamente enfermos;

- Objetivo 3: investigar o efeito da adição de um protocolo de EENM precoce e de curto prazo à terapia convencional na variação da espessura e ecointensidade muscular em indivíduos politraumatizados criticamente enfermos, bem como nos marcadores inflamatórios – citocinas pró e anti-inflamatórias e MMP-2 – e de sinalização da via anabólica de síntese muscular – IGF-I e MMP-9 – na corrente sanguínea.

2 ARTIGO CIENTÍFICO

2.1 ESTUDO 1 – "*RELIABILITY OF SKELETAL MUSCLE ULTRASOUND IN CRITICALLY ILL TRAUMA PATIENTS*"

RESUMO

Introdução: A ultrassonografia é um método não invasivo para avaliação da musculatura esquelética. A segurança, viabilidade e reprodutibilidade ainda não foram avaliados em indivíduos politraumatizados criticamente enfermos, após admissão na Unidade de Emergência.

Métodos: Dois examinadores (*expert* e sem experiência) adquiriram imagens sonográficas em dez pacientes; um analista experiente, cego quantificou as imagens. Em um grupo separado de dez pacientes, dois analistas (*expert* e sem experiência) quantificaram a espessura e ecointensidade (método quadrado ou traçado) do músculo quadríceps em imagens adquiridas por um examinador.

Resultados: Excelente reprodutibilidade foi encontrada tanto para aquisição quanto para a análise das imagens (coeficientes de correlação intraclasse >0.987; p<0.001). Os valores de Erro Padrão da Média variaram de 0.01-0.06cm para espessura muscular, e de 0.75-2.04 AU para ecointensidade muscular. Os coeficientes de variação foram <6% para espessura e ecointensidade. Os valores de ecointensidade medidos pelo método do quadrado foram maiores do que pelo traçado (p=0.003).

Conclusões: A ultrassonografia é um método seguro, factível e confiável para avaliação muscular em indivíduos politraumatizados criticamente enfermos, independente do nível de experiência do examinador.

2.2 ESTUDO 2 – "*ACUTE SKELETAL MUSCLE WASTING ASSESSED WITH ULTRASOUND AND MEDIATORS OF MUSCLE GROWTH AND SYSTEMIC INFLAMMATION IN CRITICALLY ILL TRAUMA PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY*"

RESUMO

Contexto: O dano muscular esquelético já foi demonstrado em indivíduos internados em UTI; entretanto, politraumatizados são geralmente jovens e previamente saudáveis, mas estão expostos à inflamação e inatividade desde o momento pré-hospitalar, o que pode levar a uma deterioração muscular precoce e mais grave. O objetivo desse estudo é descrever, pela primeira vez em politraumatizados criticamente enfermos, mudanças precoces na espessura e ecointensidade muscular, e mediadores de sinalização de crescimento muscular e inflamação sistêmica.

Métodos: Um estudo prospectivo observacional foi conduzido na Unidade de Emergência, Sala de Recuperação Pós-Anestésica e Unidade de Terapia Intensiva de um hospital público com um Centro de Trauma Nível I. Adultos politraumatizados em ventilação mecânica foram avaliados para elegibilidade nas primeiras 24 horas após admissão na Emergência. Todos os pacientes receberam tratamento de reabilitação padrão, consistindo de fisioterapia respiratória e mobilização progressiva duas vezes ao dia. Para avaliar o dano muscular, foram obtidos por cinco dias consecutivos medidas sonográficas de ecointensidade e espessura muscular, e níveis séricos de insulin-like growth factor I (IGF-I) e citocinas inflamatórias. As mudanças ao longo do tempo foram avaliadas por medidas repetidas de análise de variância, com um teste post hoc de Bonferonni. As relações bivariadas entre ultrassonografia, medidas sanguíneas e resultados clínicos foram avaliadas pelo coeficiente de Pearson ou Spearman, como apropriado.

Resultados: Ao longo de cinco dias, foram observados um aumento de 32% (62.1±13.1 para 80.4±17.3AU, $p<0.0001$) na ecointensidade do Reto Femoral e uma redução de 11% (3.91±0.86 para 3.47±0.64cm, $p=0.01$) na espessura do quadríceps. Os níveis séricos de IGF-I diminuíram 39% (68.8±43.6 para 42.4±29.4ng/mL, $p=0.01$). Os níveis de citocina anti-inflamatória IL-4 apresentaram uma redução de 12%

(3.99±0.63 para 3.51±0.73pg/mL, p=0.02) no dia 2 comparado ao dia 1, enquanto os níveis de citocinas pró-inflamatórias aumentaram – IL-2, 6% (8.31±0.81 para 8.82±0.96ng/mL, p=0.01) do dia 1 para o dia 3 e IFN-y, 17% (4.83±1.39 para 5.66±1.61pg/mL, p=0.02) do dia 1 para o dia 5.

Conclusões: Mudanças significativas na espessura e ecointensidade muscular iniciam-se já em 48 horas após a admissão hospitalar e intensificam-se ao longo de 5 dias de hospitalização em indivíduos politraumatizados criticamente enfermos; a redução nos níveis séricos de IGF-I e as alterações nas citocinas sugerem um estimulo reduzido ao crescimento muscular e um processo inflamatório intenso e precoce nesse curto período de doença crítica, apesar do tratamento de reabilitação oferecido.

2.3 ESTUDO 3 – "*NEUROMUSCULAR ELECTRICAL STIMULATION ALLEVIATES MUSCLE WASTING IN CRITICALLY ILL TRAUMA PATIENTS: A RANDOMIZED CONTROLLED TRIAL*"

RESUMO

Propósito: Indivíduos politraumatizados criticamente enfermos experimentam inflamação e inatividade precoce, que podem induzir mudanças agudas na musculatura esquelética. A Estimulação elétrica neuromuscular (EENM) pode ser benéfica a esses pacientes; entretanto, seus efeitos na espessura e ecointensidade muscular, bem como os biomarcadores envolvidos na síntese muscular e degradação proteica, ainda são controversos na literatura. Esse ensaio clínico randomizado investiga se um protocolo precoce e de curto prazo de EENM é efetivo para aliviar o dano muscular em indivíduos politraumatizados criticamente enfermos.

Métodos: Quarenta indivíduos sob ventilação mecânica devido a politrauma foram prospectivamente recrutados nas primeiras 24 horas após a admissão na Emergência. O grupo intervenção (n=20) recebeu umas sessão diária de EENM bilateral no musculo quadríceps, por cinco dias consecutivos, enquanto o grupo controle (n=20) recebeu apenas o tratamento convencional. A espessura e ecointensidade muscular foram avaliadas diariamente por ultrassonografia. Mediadores de sinalização do crescimento muscular – insulin-like growth factor I (IGF-I) and metaloproteinase de matriz (MMP)-2, e inflamação – citocinas e MMP-9, foram quantificados em amostras sanguíneas.

Resultados: Comparando o sétimo dia ao primeiro dia, o grupo EENM teve ecointensidade ($p<0.0001$) e espessura ($p=0.006$) melhor preservadas em comparação ao grupo controle. O grupo EENM também apresentou uma menor redução nos níveis séricos de IGF-I ($p=0.03$) e MMP-2 ($p=0.005$), um maior aumento nos níveis de IL-4 ($p=0.01$), um menor aumento no IFN-y ($p=0.02$), uma redução no TNF- α ($p=0.004$) e na MMP-9 ($p=0.005$).

Conclusões: A EENM é uma estratégia efetiva para preservar a ecointensidade e espessura muscular, atenuando o declínio nos mediadores de crescimento muscular

e promovendo uma melhor regulação do balanço inflamatório em indivíduos politraumatizados criticamente enfermos.

3 DISCUSSÃO GERAL E CONCLUSÕES

3.1 INTEGRAÇÃO DAS PARTES DO PROJETO

A miopatia do paciente crítico e a consequente deterioração funcional vem sendo amplamente estudadas (13, 25, 62). No entanto, a avaliação muscular precoce ainda é intrigante, principalmente em indivíduos sedados ou que não são capazes de cooperar com um teste volicional (63), ou em ambientes desafiadores como a Unidade de Emergência (64). No primeiro estudo, observamos que a avaliação da espessura e ecointensidade muscular nas primeiras 24 horas após admissão hospitalar na Unidade de Emergência é segura e viável em indivíduos politraumatizados criticamente enfermos, com excelente reprodutibilidade tanto para a aquisição quanto para a análise das imagens. As imagens sonográficas foram adquiridas em menos de dez minutos, em acordo com estudos prévios no ambiente de terapia intensiva (63, 65). Mesmo entre avaliadores com diferentes níveis de experiência, é possível padronizar essa medida com um breve treinamento de 20 minutos, conforme previamente demonstrado em indivíduos saudáveis (66).

A ultrassonografia muscular representa uma modalidade atrativa em diferentes ambientes de cuidados críticos, uma vez que é segura, facilmente aplicável, não invasiva e pode ser realizada próximo à admissão hospitalar, de forma mais precoce que outros testes que dependam da cooperação do paciente. As medidas de espessura e ecointensidade podem potencialmente ser utilizadas tanto para diagnóstico muscular quanto para avaliar a efetividade de intervenções em pacientes criticamente enfermos.

A ecointensidade foi significativamente maior quando quantificada pelo método quadrado em comparação com o método traçado; além disso, um menor coeficiente de variação foi encontrado quando a região de interesse foi selecionada pelo método quadrado, sugerindo que a técnica do quadrado deve ser escolhida para a análise da ecointensidade da musculatura periférica. Tais variações reforçam a necessidade de padronizar os protocolos e configurações para realização de ultrassonografia

muscular, para que os resultados possam ser utilizados para guiar a prática clínica e para a realização de futuras metanálises.

O principal resultado do segundo estudo foi a demonstração de que a deterioração da espessura e ecointensidade muscular inicia-se de forma realmente precoce em indivíduos politraumatizados criticamente enfermos, já nas primeiras 24 horas após a admissão hospitalar, e persiste ao longo dos cinco primeiros dias de hospitalização, apesar de um tratamento de reabilitação padrão. De acordo com esses achados, as medidas de espessura e ecointensidade devem ser realizadas o mais próximo possível à admissão hospitalar, ou uma quantidade significativa de mudança pode ser subestimada.

Os estudos em pacientes críticos utilizam primariamente a espessura (65, 67, 68) ou área de secção transversa (26, 69) muscular; recentemente, a ecointensidade começou também a ser avaliada (63, 70). A ecointensidade, independente da massa muscular, relaciona-se negativamente com a força (71) e performance (72) muscular em idosos, e aumenta com a idade em função de substituição muscular por gordura e tecido fibroso (73) Uma forte correlação entre ecointensidade e tecido fibroso/gordura intramuscular já foi descrita previamente em indivíduos saudáveis (74), idosos (75) e indivíduos com doenças neuromusculares (76). Puthucheary e colaboradores (70) demonstraram por meio de biopsia que mudanças na ecointensidade refletem a ruptura da arquitetura muscular em nível celular em doentes críticos, também observada em pacientes com sepse grave (77).

Em nosso estudo, a ecointensidade muscular aumentou ao longo dos cinco primeiros dias. Entretanto, apesar da redução no segundo e no quinto dia em comparação ao primeiro dia de hospitalização, a espessura muscular não variou significativamente no terceiro e no quarto dia. Em indivíduos saudáveis sob imobilização, Wall e colaboradores (30) observaram uma redução de 3.5% na massa muscular do quadríceps no quinto dia. Em doentes críticos, Puthucheary e colaboradores (26) demonstraram uma redução de 12.5% na área de secção transversa do Reto Femoral no sétimo dia após admissão na UTI; já Parry e colaboradores (63) descreveram uma redução na espessura do Reto Femoral de 16.6% no quinto dia. Por outro lado, Fischer e colaboradores (67) observaram um aumento na espessura muscular do quadríceps nos três primeiros dias após cirurgia

cardio-torácica em indivíduos criticamente enfermos, com uma correlação positiva entre as mudanças na espessura muscular e o balanço hídrico cumulativo. Em nosso estudo, não observamos correlação entre balanço hídrico e ecointensidade; no entanto, a espessura muscular correlacionou-se com o balanço acumulado no quarto e quinto dia. Em indivíduos com sepse grave, a ecointensidade aumentou mesmo na presença de balanço hídrico negativo, com dano estrutural especifico na arquitetura muscular (77). Tais achados sugerem que a ecointensidade e a espessura são impactadas de forma diferente pelo acúmulo de fluido intramuscular, e podem refletir mudanças diferentes na arquitetura muscular, devendo portanto ser avaliadas e acompanhadas em pacientes críticos.

Observamos em nosso estudo que os níveis séricos de IGF-I diminuíram nesse curto período de doença crítica, sugerindo que a ausência de carga mecânica inibe a via de crescimento muscular nesses pacientes. IL-4, uma citocina anti-inflamatória, diminuiu no segundo dia, enquanto as citocinas pró-inflamatórias aumentaram – IL-2 no terceiro dia e IFN-y ao longo dos cinco dias. Foi observado ainda uma forte correlação negativa entre mudanças nos níveis séricos de IL-6 e ecointensidade muscular, o que suporta o impacto das citocinas pró-inflamatórias (e do estado inflamatório dos primeiros dias de doença crítica) na deterioração da qualidade muscular.

Os resultados encontrados no terceiro estudo demonstram que um protocolo precoce e de curto prazo de EENM é uma estratégia efetiva para preservar a ecointensidade e espessura muscular em indivíduos politraumatizados criticamente enfermos. Além disso, a menor redução observada nos níveis séricos de IGF-I e MMP-2 sinalizam um menor impacto da inatividade e da doença critica nas vias de sinalização anabólica muscular, enquanto as mudanças nos níveis de citocinas e na MMP-9 sugerem que a EENM promove um balanço pró e anti-inflamatório mais favorável, minimizando a degradação muscular mediada pelo processo anti-inflamatório.

Já foi demonstrado que mudanças moleculares associadas com a atrofia induzida pelo desuso podem ser prevenidas pela EENM em indivíduos completamente sedados (57) e em indivíduos saudáveis sob imobilização (78); mesmo uma única sessão de EENM estimula a síntese muscular proteica em indivíduos idosos com

diabetes (79). No entanto, em alguns estudos que utilizaram um protocolo de EENM, não foi possível preservar o trofismo muscular após cirurgia cardiotorácica (67) ou em indivíduos com sepse grave (80). A diferença nos resultados pode estar relacionada ao perfil do paciente ou ao momento de início do protocolo de eletroestimulação. Hirose e colaboradores (69) iniciaram um protocolo de EENM em indivíduos comatosos sete dias após a internação na UTI; nos indivíduos eletroestimulados, a perda de massa muscular foi interrompida, mas não foi possível recuperar a massa muscular que já havia sido perdida. Já foi demonstrado que é mais simples prevenir a perda muscular do que recuperar a musculatura perdida (81), o que reforça a necessidade de intervenções realmente precoces em indivíduos criticamente enfermos.

Algumas dificuldades em relação à efetividade da eletroestimulação em produzir contrações musculares visíveis em pacientes críticos foram previamente apontadas, devido ao aumento da impedância da pele/tecidos leves, e/ou edema (82); em nossos pacientes, apesar do balanço hídrico positivo, observamos contrações musculares efetivas em todas as sessões de eletroestimulação. Isso pode ser parcialmente atribuído à precocidade da nossa intervenção; mesmo em outros estudos que propuseram uma intervenção precoce (57, 83), o tempo médio entre a admissão na UTI e a primeira sessão de EENM variou de 2.5 a 4.6 dias; além disso, a permanência prolongada na Unidade de Emergência devido à falta de leitos de UTI é um fenômeno mundial (84), podendo levar a um atraso ainda maior no inicio do tratamento. Já foi descrito que os pacientes respondem melhor à EENM no início de sua internação na UTI em comparação a uma semana de tempo de permanência (82); como nosso protocolo teve início nas primeiras 24 horas após admissão hospitalar, muitas vezes ainda na Unidade de Emergência, pode ser que isso tenha aumentado a efetividade da eletroestimulação em prevenir o dano muscular.

3.2 DETALHES DA EXECUÇÃO DO PROJETO

A população alvo do projeto foram indivíduos politraumatizados, admitidos nas primeiras 24 horas de ventilação mecânica, e acompanhados por sete dias consecutivos. O estudo foi realizado em diversos ambientes hospitalares, como o Centro de Trauma / Pronto Socorro, Unidade de Suporte Avançado ao Trauma /

Pronto Socorro, Sala de Recuperação Pós-Anestésica / Centro Cirúrgico, e Unidade de Terapia Intensiva – Trauma.

Em todas essas unidades, foi necessário o envolvimento de toda a equipe multidisciplinar de suporte ao paciente (fisioterapeutas, médicos, enfermeiros e técnicos). Realizar a coleta em diferentes ambientes hospitalares, e solicitar aos familiares a autorização para a realização da pesquisa nas primeiras 24 horas após a admissão hospitalar, foi realmente desafiador. No entanto, apenas duas famílias não concordaram com a inclusão na pesquisa.

Não foi possível coletar amostras sanguíneas de todos os pacientes em todos os *time points*, devido a contraindicação clínica. Embora não tenhamos encontrado dificuldades técnicas para realizar a ultrassonografia, observamos uma variação diária na espessura muscular, que pode ter ou não impacto funcional. Futuros estudos correlacionando as alterações na estrutura muscular com marcadores funcionais precisam ser realizados.

A previsão inicial de coleta de dados era de doze meses, baseada no número de pacientes admitidos na Unidade de Emergência; no entanto, foi necessário ampliar o tempo de coleta para dezoito meses até atingir o cálculo amostral, em função principalmente do número de pacientes excluídos por suspeita clinica de morte encefálica.

3.3 CONCLUSÕES

A ultrassonografia muscular constitui uma ferramenta para avaliação muscular segura e facilmente aplicável em indivíduos politraumatizados criticamente enfermos, representando uma modalidade atrativa em diferentes ambientes de cuidados críticos. O protocolo de ultrassom proposto apresentou excelente reprodutibilidade intra e inter-examinador após uma breve sessão de treinamento de 20 minutos, tanto para a aquisição quanto para a análise das imagens, independente do nível de experiência prévia do examinador.

Ao avaliar indivíduos politraumatizados criticamente enfermos, observou-se um aumento na ecointensidade muscular e uma redução na espessura muscular em

apenas 48 horas após a admissão hospitalar, mesmo com um tratamento padrão de reabilitação. a redução nos níveis séricos de IGF-I sugere uma inibição precoce nas vias de sinalização de hipertrofia muscular, e as alterações nos níveis de citocinas reforça a relevância da inflamação sistêmica no dano muscular já nesse curto período de doença crítica. A ecointensidade e a espessura muscular apresentaram diferentes padrões de alteração ao longo de cinco dias, apresentam apenas uma fraca correlação, e são afetadas de forma diferente pelo balanço hídrico acumulado, sugerindo que ambas as medidas devem ser realizadas para melhor avaliar a estrutura muscular em pacientes críticos.

Um protocolo de EENM precoce e de curto prazo representa uma estratégia de intervenção efetiva para prevenir o dano muscular esquelético e para preservar a espessura e ecointensidade muscular em indivíduos politraumatizados criticamente enfermos, o que pode ser atribuído à preservação da via anabólica de crescimento muscular por meio do IGF-I e da MMP-2, e a um balanço pró- e anti-inflamatório mais favorável, com menor ativação da MMP-9.

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Apêndice A – Termo de Consentimento Livre e Esclarecido (TCLE)

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O (a) Senhor (a) está sendo convidado (a) a participar do projeto: **"Estimulação elétrica neuromuscular do quadríceps em indivíduos politraumatizados sob ventilação mecânica".**

O nosso objetivo é **analisar o efeito da estimulação elétrica neuromuscular na função muscular periférica de indivíduos politraumatizados admitidos na UTI com necessidade de ventilação mecânica, além de identificar as alterações ocorridas na estrutura muscular desses indivíduos.**

O(a) senhor(a) receberá todos os esclarecimentos necessários antes e no decorrer da pesquisa e lhe asseguramos que seu nome não aparecerá sendo mantido o mais rigoroso sigilo através da omissão total de quaisquer informações que permitam identificá-lo(a)

As medidas serão realizadas no período de internação na UTI, não implicando em qualquer risco ou dano adicional não controlado ao paciente. Informamos que, a qualquer momento, o (a) Senhor (a) pode se recusar a participar ou continuar na pesquisa, não implicando em qualquer prejuízo ao atendimento. Asseguramos que o nome dos indivíduos pesquisados não aparecerá, sendo mantido o mais rigoroso sigilo através da omissão total de quaisquer informações que permitam identificá-lo (a).

Os resultados da pesquisa serão apresentados em forma de tese de doutoramento, podendo inclusive ser publicados posteriormente. Os dados e materiais utilizados na pesquisa ficarão sobre a guarda do pesquisador.

Se o (a) Senhor (a) tiver qualquer dúvida em relação à pesquisa, por favor, telefone para: **Dra. Luciana Vieira,** fisioterapeuta do Hospital de Base do Distrito Federal, telefone: (61) 8151-1027 das 08 às 12 horas de segunda à sexta-feira.

Este projeto foi Aprovado pelo Comitê de Ética em Pesquisa da SES/DF. Qualquer dúvida com relação à assinatura do TCLE ou sobre os direitos do sujeito da pesquisa podem ser obtidos através do telefone: (61) 3325-4955.

Este documento foi elaborado em duas vias, uma ficará com o pesquisador responsável e a outra com o sujeito da pesquisa.

_____

Nome / assinatura

_____

Pesquisador Responsável

Brasília, ___ de _____de _____

Apêndice B – Contribuições Cientificas

MANUSCRITOS SUBMETIDOS (PRIMEIRO AUTOR)

1. **Vieira, L**; Cipriano Jr, G; Chiappa, AMG; Cipriano, GFB; Vieira, PJC; Zago, JG; Castilhos, M; Santos, FV; Chiappa, GR. Combined effect of neuromuscular electrical stimulation on mobilization decreases duration of mechanical ventilation: a randomized controlled trial. Submetido a revista *Physiotherapy Theory and Practice* em 16 de Abril de 2016.

2. **Vieira, L**; Melo, P; Maldaner, V; Durigan, JL; Araujo, CN; Souza, VC; Chiappa, G; Mathur, S; Burtin, C; Cipriano Jr, G. Acute skeletal muscle wasting assessed with ultrasound and mediators of muscle growth and systemic inflammation in critically ill trauma patients: a prospective observational study. Submetido a revista *Critical Care* em 06 de Julho de 2016.

3. **Vieira, L**; Mathur, S; Santana, L; Melo, P; Maldaner, V; Silva, PR; Durigan, JL; Cipriano Jr, G. Reliability of skeletal muscle ultrasound in critically ill trauma patients. Submetido a revista *Muscle&Nerve* em 27 de Agosto de 2016.

4. **Vieira, L**; Mathur, S; Burtin, C; Melo, P; Durigan, JQ; Marqueti, RC; Silva, PE; Nobrega, OT; Barin, FR; Machado-Silva, W; Cipriano Jr, G. Neuromuscular electrical stimulation alleviates muscle wasting in critically ill trauma patients: a randomized controlled trial. Submetido a revista *Intensive Care Medicine* em 28 de Agosto de 2016.

MANUSCRITOS SUBMETIDOS (AUTOR COLABORADOR)

1. Silva, PE; Maldaner, V; Gomes, H; **Vieira, L**; Melo, P; Babaut, N; Cipriano Jr, G; Durigan, JLQ. Neuromuscular excitability dysfunction is associated with early detection of muscle atrophy in mechanically-ventilated traumatic brain injury patients. Submetido a revista *Intensive Care Medicine* em 21 de Abril de 2016.

2. Wickerson, L; Rozenberg, D; Janaudis-Ferreira, T; Deliva, R; Lo, V; Beauchamp, G; Helm, D; Gottesman, C; Mendes, P; **Vieira, L**; Herridge, M; Singer, LG; Mathur, S. Physical rehabilitation for lung transplant candidates and recipients: an evidence-informed clinical approach. Submetido a revista *World Journal of Transplantation* em 27 de Abril de 2016; aceito para publicação em 17 de Agosto de 2016.

3. Rozenberg, D; Martelli, V; **Vieira, L**; Orchanian-Cheff, A; Keshwani, N; Singer, LG; Mathur, S. Assessment of Peripheral Skeletal Muscle Size and Quality in Chronic Lung Disease: A Systematic Review. Submetido a revista *Chest* em 18 de Maio de 2016.

MANUSCRITOS EM ELABORAÇÃO (PRIMEIRO AUTOR)

1. **Vieira, L**; Mendes, P; Mathur, S; Melo, P; Cipriano Jr, G. Is there enough evidence for Neuromuscular Electrical Stimulation in Critically Ill Patients? A Systematic Review and Meta-Analysis? A Systematic Review and Meta-Analysis.

2. **Vieira, L**; Phadke, CP; Boulias, C; Ismail, F; Cipriano Jr, G; Mathur, S. Impact of passive cycling in persons with spinal cord injury: a Systematic Review.

RESUMOS APRESENTADOS EM CONGRESSOS E PUBLICADOS EM PERIÓDICOS INDEXADOS (PRIMEIRO AUTOR)

1. **Vieira, L**; Cipriano, G; Silva, VZM; Lima, L; Melo, PF; Garbero, R. *Noninvasive Ventilation In Emergency Department: Predictors Of Success Or Failure.* Poster Discussion Session. American Thoracic Society (ATS) Conference. San Diego, CA, USA. May 18, 2014. Resumo publicado em **Am J Respir Crit Care Med 189;2014:A1180**

2. **Vieira, L**; Garbero, R; Rocha, B; Lima, L; Borges, M; Caldas, A.; Cipriano, G; Ponzio, E. *Reexpansion Pulmonary Edema Treated With Noninvasive Ventilation In Emergency Department*. Poster Discussion Session. American

Thoracic Society (ATS) Conference. San Diego, CA, USA. May 21, 2014. Resumo publicado em **Am J Respir Crit Care Med 189;2014:A6448**

3. **Vieira, L**; Cipriano, G; Silva, PE; Silva, V; Melo, P; Durigan, J; Santana, LV; Lucilia, N; Xavier, A; Gomes, H. *Neuromuscular electrical stimulation in mechanically ventilated polytrauma patients: A strategy to minimize musculoskeletal dysfunction.* Oral presentation. European Respiratory Society (ERS) Congress. Amsterdam, Netherlands. September, 2015. Resumo publicado em **European Respiratory Journal 2015 46: OA3265**

4. **Vieira, L**; Melo, P; Maldaner, V; Xavier, A; Souza, VC; Silva, PE; Mathur, S; Cipriano Jr, G. *Skeletal Muscle Atrophy Occurs Early And Rapidly In The First 5 Days After Emergency Admission In Mechanically Ventilated Polytrauma Patients.* Poster Discussion Session. American Thoracic Society (ATS) Conference. San Francisco, CA, USA. May 16, 2016. Resumo publicado em **Am J Respir Crit Care Med 193;2016:A4517**

5. **Vieira, L**; Melo, P; Maldaner, V; Santana, LV; Nobrega, OT; Durigan, J; Mathur, S; Cipriano Jr, G. *Early Neuromuscular Electrical Stimulation Preserves Skeletal Muscle Size And Echogenicity In Mechanically Ventilated Polytrauma Patients*. Poster Discussion Session. American Thoracic Society (ATS) Conference. San Francisco, CA, USA. May 16, 2016. Resumo publicado em **Am J Respir Crit Care Med 193;2016:A4518**

RESUMOS APRESENTADOS EM CONGRESSOS E PUBLICADOS EM PERIÓDICOS INDEXADOS (AUTOR COLABORADOR)

1. Melo, PF; Durigan, J; **Urache, L**; Silva, P; Lemos, B; Filho, J; Carvalho, V; Oliveira, T; Cipriano, G; Silva, VM. *The Measurement Of Chronaxie And Rheobase In Patients With Polineuromyopathy Of Critical Illness*. Thematic Poster Session. American Thoracic Society (ATS) Conference. San Diego, CA, USA. May 20, 2014. Resumo publicado em **Am J Respir Crit Care Med 189;2014:A4512**

2. Melo, PF; Silva, V; Cirpiano, G; Lima, A; Campos, F; Cahalin, L; Arena, R; **Tavernard, L**. *Relationship Between Physical Activity Patterns And Key Cardiopulmonary Exercise Testing Variables In Patients With Heart Failure*. Thematic Poster Session. American Thoracic Society (ATS) Conference. San Diego, CA, USA. May 21, 2014. Resumo publicado em **Am J Respir Crit Care Med 189;2014:A5852**

3. Melo, PF; **Urache, L**; Silva, VZM; Chaves Filho, F; Lima, LF; Silva, ML; Nakata, CH; Cipriano Jr, G. *Fisioterapia na Sala de Recuperação Pós-Anestésica de um hospital público terciário no Distrito Federal*. Poster. Simposio Internacional de Fisioterapia Cardio-Respiratória e Fisioterapia em Terapia Intensiva (SIFR). Salvador, BA, Brasil. 4 de Setembro de 2014. Resumo publicado em **ASSOBRAFIR Ciência. 2014 Set;5(Supl 1):13-83**

4. Melo, PF; **Urache, L**; Silva, VZM; Cipriano Jr, G; Nakata, CH; Silva, ML; Carvalho, DB; Lima, LF. *Avaliação do conhecimento dos fisioterapeutas da UTI de um hospital público terciário do Distrito Federal, em relação à elevação adequada da cabeceira do leito*. Poster. Simposio Internacional de Fisioterapia Cardio-Respiratória e Fisioterapia em Terapia Intensiva (SIFR). Salvador, BA, Brasil. 5 de Setembro de 2014. Resumo publicado em **ASSOBRAFIR Ciência. 2014 Set;5(Supl 1):13-83**

5. Melo, PF; **Urache, L**; Silva, VZM; Cipriano Jr, G; Chaves Filho, F Nakata, CH; Lima, LF; Silva, ML. *Alteração das características da ventilação mecânica pós criação de um serviço de fisioterapia na Sala de Recuperação Pós Anestésica em um hospital público terciário do Distrito Federal.* Poster. Simposio Internacional de Fisioterapia Cardio-Respiratória e Fisioterapia em Terapia Intensiva (SIFR). Salvador, BA, Brasil. 5 de Setembro de 2014. Resumo publicado em **ASSOBRAFIR Ciência. 2014 Set;5(Supl 1):13-83**

6. Nakata, CH; Teixeira, FA; **Vieira, L**; Silva, ML; Thomaz, SR; Lima, ACGB; Lima, FVSO; Borges, RF; Cipriano Jr, G. *Acute effects of interferential electrical stimulation on heart rate variability in healthy women.* Poster. American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) Annual Meeting. Washington, DC, USA. September 3, 2015. Resumo publicado em **Journal of Cardiopulmonary Rehabilitation & Prevention 2015;35:286-294**

7. Santana, L; Pinto, N; Souza, A; Andrade, M; Silva, P; **Vieira, L**; Cipriano Jr, G; Durigan, JL; Maldaner, V. *Assessing electrically quadriceps induced torque in critically ill patients.* Poster. European Respiratory Society (ERS) Congress. Amsterdam, Netherlands. September, 2015. Resumo publicado em **European Respiratory Journal 2015 46: PA4814**

8. Silva, V; Santana, L; Pinto, N; Durigan, JL; Cipriano, G; **Urache, L**; Silva, PE. *Reliability of hand-held dynamometer for assessment of electrically induced torque in critically ill patients*. Poster. European Respiratory Society (ERS) Congress. Amsterdam, Netherlands. September, 2015. Resumo publicado em **European Respiratory Journal 2015 46: PA4815**

9. Silva, VM; Cipriano Jr, G; Durigan, J; Machado, M; Silva, P; Melo, P; **Urache, L**. *A Novel Noninvasive Method For Measuring Peripheral Muscle Strength In Fully Sedated Critically Ill Patients*. Poster Discussion Session. American Thoracic Society (ATS) Conference. San Francisco, CA, USA. May 15, 2016. Resumo publicado em **Am J Respir Crit Care Med 193;2016:A1156**

10. Santana, LV; Pinto, N; Xavier, A; Maldaner, V; Melo, P; Silva, PE; Cipriano Jr, G; Durigan, J; **Vieira, L**; Zille, R. *Interobserver Reliability Of Quadriceps Evaluation By Ultrasound In Mechanically Ventilated Polytrauma Patients.* Thematic Poster Session. American Thoracic Society (ATS) Conference. San Francisco, CA, USA. May 16, 2016. Resumo publicado em **Am J Respir Crit Care Med 193;2016:A4006**

11. Silva, PE; Carvalho, KL; Araujo, AE; Castro, JD; **Vieira, L**; Melo, P; Pereira, L; Nunes, L; Santos, M; Babaut, N; Maldaner, V; Durigan, RCM; Cipriano Jr, G; Durigan, JL. *Early detection of muscle atrophy in mechanically-ventilated patients.* Poster. Simposio Internacional de Fisioterapia Cardio-Respiratória e Fisioterapia em Terapia Intensiva (SIFR). Belo Horizonte, MG, Brasil. 11 de Junho de 2016. Resumo publicado em **ASSOBRAFIR Ciência. 2016 Jun;7(Supl 1):29-94**

12. Campos, FVS; Lima, ACG; Melo, PF; Silva, VZM; **Urache, L**; Cipriano, GFB; Cipriano Jr, G. *Efeitos da ventilação não invasiva durante exercício isocinético em pacientes com insuficiência cardíaca*. Poster. Simposio Internacional de

Fisioterapia Cardio-Respiratória e Fisioterapia em Terapia Intensiva (SIFR). Belo Horizonte, MG, Brasil. 11 de Junho de 2016. Resumo publicado em **ASSOBRAFIR Ciência. 2016 Jun;7(Supl 1):29-94**

FINANCIAMENTO

O presente projeto foi realizado com recursos do edital Universal do Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq 487.177/2013-4); do edital da Fundação de Ensino e Pesquisa em Ciências da Saúde (FEPECS 41/2013); e do edital Fundação de Amparo a Pesquisa do Distrito Federal (FAP-DF 193.000.862/2014). A autora realizou Programa de Doutorado Sanduíche no Exterior com recursos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, PDSE - 99999.004044/2015-00).

Apêndice C – Programa de Doutorado Sanduíche no Exterior (PDSE)

LOCAL

University of Toronto

Department of Physical Therapy

Muscle Function & Performance Research Lab

Toronto, Ontario, Canada

PERÍODO

01 de agosto de 2015 a 31 de julho de 2016.

PROCESSO

CAPES, PDSE - 99999.004044/2015-00

CO-ADVISOR

Dr Sunita Mathur

BScPT, MSc, PhD

Assistant Professor

> "Sunita Mathur is a physiotherapist and Assistant Professor in the Dept of Physical Therapy. She completed her BSc in physiotherapy and MSc from Dalhousie University, PhD in Human Kinetics (Exercise Physiology) from the University of British Columbia, and a post-doctoral fellowship at the University of Florida.
>
> Sunita leads the Muscle Function and Performance Lab in the Dept of Physical Therapy. She is also the co-founder and co-Chair of the Canadian Network for Rehabilitation and Exercise for Solid Organ Transplant Optimal Recovery (CAN-RESTORE).

More information about CAN-RESTORE can be found at www.cntrp.ca/exercise

Sunita is also a member of the Cardiorespiratory Division of the Canadian Physiotherapy Association, the Canadian Respiratory Health Professionals of The Lung Association **and the Canadian Society of Exercise Physiology."**

http://www.physicaltherapy.utoronto.ca/faculty/sunita-mathur/

ATIVIDADES REALIZADAS

Auxílio em coleta de dados de protocolos

1. Understanding the progression of skeletal muscle dysfunction in lung transplant recipients

   Dr Lianne Singer, Polyana Mendes, Dr. Sunita Mathur, Dr. Dina Brooks, Lisa Wickerson, Denise Helm

2. CYCLE Pilot: A Pilot Randomized Study of Early Cycle Ergometry Versus Routine Physiotherapy in Mechanically Ventilated Patients

   Dr Michelle Kho, Alex Molloy, Dr Sunita Mathur, Vince Lo

Lab Meetings & Journal Clubs semanais

CURSOS REALIZADOS

English Language & Writing Support

1. Academic Conversation Skills

   This course is for non-native speakers of English who wish to improve their listening and speaking skills in order to communicate more effectively in an academic environment. If you have difficulty participating in class discussion or speaking to your classmates and professors, this course is designed to meet your needs. Over six weeks, participants will gain confidence as they develop their ability to engage in academic dialogue. Through a series of class exercises that require active student participation, ACS focuses on topics such as how to present your ideas orally, how to disagree respectfully, and how to manage conversations sensitively.

Course duration: 6 weeks.

2. Prewriting Strategies for Developing and Organizing Your Ideas

In order for a research paper to be clear to readers, it must first be crystal clear in the mind of its author. Whether you are writing a course paper, a journal article, or a thesis, this course will help you clarify in your own mind the content and structure of your argument before you begin to write. Participants will be introduced to a range of strategies for developing and organizing their ideas – strategies such as organizing notes through key words, outlining, diagramming, use of Aristotle's Topics, etc. – and will be encouraged to consider which strategies work best given their own learning styles. Drawing on techniques from classical rhetoric, the course will give students the chance to practice strategies for investigating and organizing ideas at both the pre-writing and mid-writing stages. The course is designed for graduate students in the physical and life sciences.

Course duration: 4 weeks.

3. Academic Writing 1: Focus on Essentials

This class is designed for non-native speakers of English who wish to improve the overall quality of their academic writing. Students will learn to improve the formality of their writing; to make claims commensurate with their evidence; to create coherent paragraphs; to develop clear transitions; to enhance their academic vocabulary; to understand the correct use of verb tense in academic writing; and, overall, to see how academic writing in their new context may differ from writing they have done in the past. The goal of the course is to show graduate students some key strategies to improve their academic writing. This course is the first in our Academic Writing sequence; the second course—Academic Writing 2: Focus on Grammar—deals with grammatical issues and the third—Academic Writing 3: Focus on Style—tackles more sophisticated issues of style.

Course duration: 5 weeks.

4. Academic Writing 2: Focus on Grammar

This course is designed for non-native speakers of English who wish to improve the grammatical correctness of their academic writing and understand the way grammatical structures are used in academic writing at the graduate level. Students will learn to self-diagnose their most common grammatical errors, to apply the key grammatical rules learned throughout the course, to develop strategies to enhance grammatical correctness, and to identify resources for improving their grammar. Specific topic areas covered in the course include maintaining subject-verb agreement, minimizing article errors, using relative clauses correctly, avoiding punctuation errors, and clarifying incorrect or vague pronoun references.

Course duration: 5 weeks.

5. Academic Writing 3: Focus on Style

The most advanced in our Academic Writing sequence, this course is designed for non-native speakers of English who wish to improve the style of their academic writing. The course helps students use their existing linguistic sensitivity to answer a number of key questions. How do the stylistic tendencies of English differ from those of other languages? How can writers accurately describe the work and ideas of other scholars without losing the clarity of their own voices? What strategies can writers use to produce smooth, readable texts that guide the reader from sentence to sentence, from paragraph to paragraph, and from chapter to chapter? Academic Writing 3: Focus on Style assumes that students already understand the essential attributes of academic writing at the graduate level and that they already have a solid command of English grammar. It is therefore strongly recommended that students take this course only after they have completed Academic Writing 1 and 2.

Course duration: 5 weeks.

6. Writing CIHR Proposals

This three-week course is open to students who are applying for CIHR (Canadian Institutes of Health Research) Master's and Doctoral Research Awards. In three two-hour classes, we will examine the specific features of successful grant proposals and bring to light common errors that lead to bad proposals. As well, we will be looking at examples of winning proposals. Students are expected to work on their own draft proposals, and individualized feedback will be available to course participants. While several of the concepts examined will also be of relevance to students applying for an Ontario Graduate Scholarship (OGS), the focus of the course is on writing an effective CIHR proposal. (Check with your department regarding your eligibility to apply for funding through CIHR and/or OGS.)

Course duration: 3 weeks.

7. Oral Presentation Skills

Does the thought of standing in front of an audience to present your work make you nervous? Would you like to present your ideas more clearly and more confidently? If the answer to these questions is yes, then this course is for you. In this course, you will receive guidance on various aspects of presenting, such as how to structure presentations, to design visual aids, to mana ge nerves, and to handle the question period. You will have a valuable opportunity to learn from the presentations of others and to practice what you learn in front of an informed and supportive audience of your peers. As a member of that audience, you will be able to practice active observing to

further improve both your listening and presenting skills. Students will have the opportunity to receive a digital recording of their own presentation.

Course duration: 5 weeks with an optional tutorial in the sixth week.

8. Research Article Boot Camp

ELWS Writing Intensives are designed to provide U of T graduate students with a dedicated time and space for intensive writing. By providing you with a writing regimen in a distraction-free environment, as well as expert support and advice, we can help you to reach your writing objectives.

Course duration: 3 full days.

TRABALHOS APRESENTADOS EM CONGRESSOS

Canadian Respiratory Conference (CRC) 2016

Halifax, Nova Scotia, Canada. April 14 - 16, 2016.

1. **Vieira, L**; Melo, P; Silva, V; Santana, LV; Amatuzzi, F; Rozenberg, D; Mathur, S; Cipriano Jr, G*. Substantial skeletal muscle loss occurs in the first 48 hours after emergency admission in mechanically ventilated polytrauma patients.* Poster. (presented)
2. Martelli, V; Rozenberg, D; **Vieira, L**; Keshwani, N; Singer, LG; Mathur, S*. A Systematic Review of Imaging Modalities to Assess Skeletal Muscle Atrophy in Chronic Lung Disease.* Poster. (presented)

Critical Care Canada Forum (CCCF) 2016

Toronto, Ontario, Canada. October 30 - November 2 2016.

1. Riegler, SE; Lee, M; Voronna, S; Dres, M; **Vieira, L**; Reid, D; Brochard L; Feguson ND; Goligher EC. Diaphragm Echogenicity in Mechanically Ventilated Patients: Measurement Precision and Preliminary Findings. Poster. (accepted)

PRÊMIO

ART SLUTSKY DAY 2016

Interdepartmental Division of Critcal Care Medicine, University of Toronto

Best Abstract Clinical Practice

Best Abstract Overall

Vieira, L; Melo, P; Maldaner, V; Santana, LV; Nobrega, OT; Durigan, J; Mathur, S; Cipriano Jr, G. *Early Neuromuscular Electrical Stimulation Preserves Skeletal Muscle Size And Echogenicity In Mechanically Ventilated Polytrauma Patients*. Oral Presentation

Anexo A – Parecer Consubstanciado do Comitê de Ética em Pesquisa da FEPECS/SES-DF

Secretaria de Estado de Saúde do Distrito Federal

COMITÊ DE ÉTICA EM PESQUISA - FEPECS/SES-DF

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Estimulação elétrica neuromuscular em pacientes com Traumatismo Crânio Encefálico sob ventilação mecânica prolongada: Ensaio Clínico Randomizado

Pesquisador: Vinicius Zacarias Maldaner da Silva

Área Temática:

Versão: 3

CAAE: 19036013.8.0000.5553

Instituição Proponente: DISTRITO FEDERAL SECRETARIA DE SAUDE

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 417.180

Data da Relatoria: 16/09/2013

Apresentação do Projeto:

Pacientes submetidos a ventilação mecânica prolongada apresentam importante perda de força muscular tanto respiratória quanto periférica com maior numero de complicações após alta das unidades de terapia intensiva. A debilidade muscular tem forte impacto no prognóstico dos indivíduos internados em UTI estando associada a internação prolongada, dificuldade no desmame da ventilação mecânica, maior mortalidade e aumento dos custos intra e extra hospitalares.

Há um crescente interesse quanto ao uso da tecnologia assistiva para minimizar os danos funcionais inerentes à permanência em UTI sendo a estimulação elétrica neuromuscular (EENM) uma delas. A EENM permite uma contração passiva da musculatura esquelética, por meio da utilização de impulsos elétricos aplicados através da pele para a musculatura a partir de eletrodos de superfície. Ela não depende da cooperação do paciente, podendo ser iniciada de forma precoce, mesmo em pacientes sedados.

O programa de EENM constitui um método seguro, de baixo custo e de ampla aplicabilidade em pacientes críticos, com grande potencial de efeitos positivos na preservação da força muscular e do status funcional também em indivíduos politraumatizados ventilados mecanicamente internados em UTI. Tais efeitos podem contribuir para a redução do tempo de desmame da ventilação mecânica e consequentemente de internação hospitalar, diminuindo o custo intra-

Endereço: SMHN 2 Qd 501 BLOCO A - FEPECS
Bairro: ASA NORTE **CEP:** 70.710-904
UF: DF **Município:** BRASILIA
Telefone: (61)3325-4955 **Fax:** (33)3325-4955 **E-mail:** comitedeetica.secretaria@gmail.com

hospitalar e os gastos do sistema de saúde.

Objetivo da Pesquisa:

Identificar as vias de sinalização intracelular e as mudanças bioquímicas responsáveis pelas alterações musculares em indivíduos politraumatizados submetidos a ventilação mecânica invasiva, por meio da análise de marcadores inflamatórios, de estresse oxidativo e zimografia;

Avaliar o efeito da inclusão de um protocolo de EENM junto ao tratamento convencional (fisioterapia respiratória, mobilização passiva e posicionamento) na função muscular periférica desses indivíduos, por meio da análise da espessura muscular e fluxo sanguíneo do quadríceps femoral;

Analisar o nível de atividade física dos indivíduos 60 dias após a alta hospitalar, por meio de acelerômetro.

Avaliação dos Riscos e Benefícios:

Benefícios: auxiliar a elucidar as características da disfunção muscular aguda, e fornecer subsídios para um programa de reabilitação precoce nesses indivíduos,minimizando a fraqueza muscular e suas consequências no status funcional.

Riscos:

São descritos riscos associados à punção venosa, tais como: hematoma, punção acidental da artéria, anemia iatrogênica, infecção e lesão nervosa. Tais riscos podem ser minimizados ou controlados, principalmente por se tratar de estudo realizado em ambiente fechado, sob supervisão contante de equipe médica, de fisioterapia e enfermagem (unidade de terapia intensiva). A dor e desconforto podem estar associados à eletroestimulação, mas tais riscos são minimizados pelo fato de o paciente estar recebendo sedo-analgesia durante o procedimento.

Comentários e Considerações sobre a Pesquisa:

Ensaio clínico randomizado e duplo cego com 20 indivíduos atendidos na Unidade de Neurotrauma do HBDF.

Critérios de inclusão: adultos (19-44 anos); com traumatismo crânioencefálico com expectativa de necessidade de ventilação mecânica invasiva por mais de 48h.

Critérios de exclusão: indivíduos com doenças neuromusculares previamente diagnosticadas; hipertensão intracraniana; amputação de membros inferiores; gravidez; com IMC acima de 40 kg/m2;em uso de fixador externo ou implantes metálicos em membros inferiores; com úlceras abertas ou lesões na pele nos pontos de aplicação dos eletrodos; portadores de marcapasso; com

trombocitopenia ou INR > 1,6 e com parada cardiorrespiratória.
Os indivíduos serão randomizados por sorteio manual em dois grupos: estudo (com NMES) e controle. Ambos os grupos receberão tratamento convencional de fisioterapia (fisioterapia respiratória + mobilização passiva através do cicloergomêtro passivo de membro inferiores e superiores).Cada indivíduo realizará duas sessões diárias de eletroestimulação, com intervalo mínimo de 6 horas entre elas. Os procedimentos serão realizados por 5 dias consecutivos. No grupo SHAM (controle), os indivíduos serão submetidos ao mesmo procedimento, entretanto a dose será ajusta em dose mínima (1 a 3 mA), a fim do equipamento esta ligado, entretanto não sendo capaz de gerar contração muscular.
A beneficência do estudo foi demonstrada.
Planilha de custos e cronograma de execução apresentados.

Considerações sobre os Termos de apresentação obrigatória:
Folha de Rosto: apresentada.
Termo de Concordância: apresentado.
TCLE: apresentado.
Currículo dos pesquisadores: apresentados

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:
Pendências atendidas.

Situação do Parecer:
Aprovado

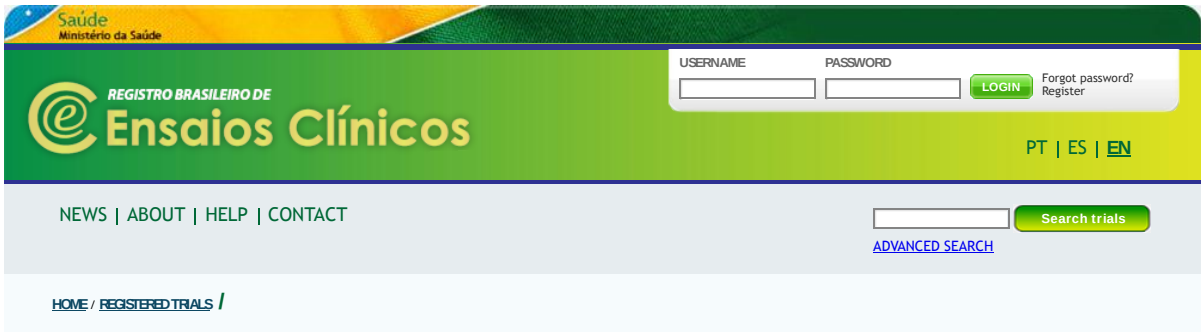
Necessita Apreciação da CONEP:
Não

Considerações Finais a critério do CEP:

BRASILIA, 07 de Outubro de 2013

Assinador por:
luiz fernando galvão salinas
(Coordenador)

Anexo B – Registro Brasileiro de Ensaios Clínicos



RBR-2dbzdy

Neuromuscular electrical stimulation in patients with Traumatic Brain Injury under prolonged mechanical ventilation: a Randomized Clinical Trial

Registration Date: June 29, 2016, 4:56 p.m.

Last Update: Aug. 23, 2016, 11:42 a.m.

Study Type:

Intervention Study

Scientific Title:

PT-BR

Estimulação elétrica neuromuscular em pacientes com Traumatismo Crânio Encefálico sob ventilação mecânica prolongada: Ensaio Clínico Randomizado

EN

Neuromuscular electrical stimulation in patients with Traumatic Brain Injury under prolonged mechanical ventilation: a Randomized Clinical Trial

Trial Identification

UTN Number: U1111-1184-8371

Public Title:

PT-BR

Eletroestimulação Neuromuscular Precoce em indivíduos politraumatizados criticamente enfermos

EN

Early Neuromuscular Electrical Stimulation in Critically Ill Trauma Patients

Scientific Acronym:

Public Acronym:

Secondary Identifying Numbers:

19036013.8.0000.5553
Issuing Authority: Plataforma Brasil - CAAE

417.180
Issuing Authority: Comitê de Ética em Pesquisa da FEPECS/SES-DF

Sponsors

Primary Sponsor: Universidade de Brasilia - Programa de Pós-Graduação em Ciências e Tecnologias em Saúde

Secondary Sponsors:

Institution: Hospital de Base do DF

Institution: Universidade de Brasilia - Programa de Pós-Graduação em Ciências e Tecnologias em Saúde

Source(s) of Monetary or Material Support:

Institution: Conselho Nacional de Desenvolvimento Tecnologico

Institution: Fundacao de Ensino e Pesquisa em Ciencias da Saude

Health Conditions

Health Condition(s) or Problem(s):

PT-BR
Traumatismo Múltiplo Unidades de Terapia Intensiva Músculo Esquelético Estimulação Elétrica

EN
Multiple Trauma Intensive Care Units Muscle, Skeletal Electric Stimulation

General Descriptors for Health Condition(s):

PT-BR
C05: Doenças musculoesqueléticas

ES
C05: Enfermedades musculoesqueléticas

EN
C05: Musculoskeletal diseases

PT-BR
V01-Y98: XX - Causas externas de morbidade e de mortalidade

EN
V01-Y98: XX - External causes of morbidity and mortality

PT-BR
M00-M99: XIII - Doenças do sistema osteomuscular e do tecido conjuntivo

EN
M00-M99: XIII - Diseases of the musculoskeletal system and connective tissue

Specific Descriptors for Health Condition(s):

PT-BR
C26.640: Traumatismo Múltiplo

ES
C26.640: Traumatismo Múltiple

EN
C26.640: Multiple Trauma

PT-BR
N02.278.388.493: Unidades de Terapia Intensiva

ES
N02.278.388.493: Unidades de Cuidados Intensivos

EN
N02.278.388.493: Intensive Care Units

PT-BR
A02.633.567: Músculo Esquelético

ES
A02.633.567: Músculo Esquelético

EN
A02.633.567: Muscle, Skeletal

PT-BR
E05.723.402: Estimulação Elétrica

ES
E05.723.402: Estimulación Eléctrica

EN
E05.723.402: Electric Stimulation

Interventions

Intervention Code(s)

Device

Interventions:

PT-BR

Grupo Intervenção (n=20): Somado ao cuidado habitual, os indivíduos randomizados no grupo NMES receberam uma sessão diária de eletroestimulação, no período vespertino, por cinco dias consecutivos (fins de semana inclusos). EENM foi realizada após avaliação por ecografia e aquisição das amostras sangüíneas. Todos os pacientes foram avaliados com referência à estabilidade fisiológica antes de cada sessão. A sessão não foi realizada se o paciente tivesse apresentado qualquer um dos seguintes sinais ou sintomas três horas antes da sessão: recebimento de bloqueador neuromuscular, acidose documentada (pH no sangue arterial <7.25), hipertensão ou hipotensão (pressão arterial média <60mmHg ou >120mmHg) ou sinais de instabilidade fisiológica (por exemplo, temperatura <34°C ou >41°C, plaquetas <20000/mm3).
Os parâmetros de eletroestimulação foram baseados na literatura disponível, de acordo com guidelines terapêuticos. EENM foi implementada simultaneamente no músculo quadriceps de ambos os membros inferiores. Após limpeza da pele, quatro e;erodes auto-adesivos retangulares (90 x 50 mm; MultiStick®, Axelgaard Manufacturing CO Ltd, Fallbrook, CA, USA) foram posicionados no ponto motor do quadriceps em cada uma das pernas. O estimulador Dualpex 071 (Quark Medical®, Piracica
ba, SP, Brazil) entrega corrente bifásica, simétrica, com ondas de pulso retangulares, a uma frequency de 50 Hz, largura de oils de 400 microsegundos, ciclo de 6 segundos on e 12 segundos off, em intensidades suficientes para evocar contracts musculares visíveis. A duracao da seesaw foi de 55 minutos incluindo 45 minutos de treinamento, com 5 minutos de aquecimento e 5 minutos de recuperação a intensidades mais baixas.
Grupo Controle (n=20): terapia convencional (fisioterapia 2x/dia)

EN

Intervention Group (n=20): In addition to usual care, patients randomized to the NMES group received one daily session of electrical stimulation, in the afternoon, for five consecutive days (weekends included). NMES was conducted after ultrasound evaluation and blood sample acquisition. All patients were screened for physiologic stability before each NMES session. The session was deferred if patients had any of the following findings within three hours before the session: received a neuromuscular blocker infusion, documented acidosis (pH by arterial blood gas <7.25), hypertension or hypotension (mean arterial pressure <60 mmHg or >120 mmHg) or signs of physiologic instability (e.g., temperature <34°C or >41°C, platelets <20000/mm3). Electrical stimulation settings were based on research available at the time of study design, in accordance with therapeutic guidelines. NMES was implemented simultaneously on the quadriceps muscles of both lower extremities. After shaving and cleaning the skin, four self-adhesive rectangular electrodes (90 x 50 mm; MultiStick®, Axelgaard Manufacturing CO Ltd, Fallbrook, CA, USA) were placed on the motor points of the quadriceps muscles of both legs. The position of the electrodes was remarked daily with an indelible marker to maintain the same location for each session. The stimulator Dualpex 071 (Quark Medical®, Piracica
ba, SP, Brazil) delivered biphasic, symmetric rectangular-wave pulses at a frequency of 50 Hz, pulse duration of 400 microseconds (?s), duty cycle of 6 seconds on (including 1 second rise time and 1 second fall time) and 12 seconds off, at intensities able to evoke visible muscle contraction. The intensity was increased if a visible muscle contraction was no longer achieved with the current intensity. The duration of the session was 55 minutes including 45 minutes of training, with 5 minutes for warm up and 5 minutes for recovery at lower intensities.
Control group (n=20): usual care (physiotherapy twice/day)

Descriptor for Intervention(s):

PT-BR

E05.723.402: Estimulação Elétrica

ES

E05.723.402: Estimulación Eléctrica

Recruitment

Recruitment Status: Data analysis completed

Recruitment Country

Brazil

Planned Date of First Enrollment: 2014-12-01

Planned Date of Last Enrollment: 2015-09-24

Target Sample Size:	Gender (inclusion sex):	Inclusion Minimum Age:	Inclusion Maximum Age:
40	-	18 Y	0 -

Inclusion Criteria:

PT-BR

Pacientes politraumatizados foram avaliados para elegibilidade nas primeiras 24 horas após admissão hospitalar. Adultos com mais de 18 anos em ventilação mecânica invasiva foram incluídos.

EN

Major trauma patients were assessed for eligibility within the first 24 hours after hospital admission. Adults older than 18 years old with invasive mechanical ventilation were included.

Exclusion Criteria:

PT-BR

gravidez; acidente vascular encefálico; doença neuromuscular prévia; suspeita de morte encefálica; amputação de membros inferiores, fratura ou lesão na pele que impedisse a avaliação por ultrassom.

EN

pregnancy; stroke; previous neuromuscular disease; suspicion of brain death; lower limb amputation, fracture or skin lesion that restrained ultrasound evaluation.

Study Type

Study Design:

PT-BR

Ensaio clínico de tratamento, paralelo, duplo cego, randomizado controlado com dois braços.

EN

Treatment Clinical trial, parallel, double blinded, randomized, controlled with two arms.

Expanded access program	Study Purpose	Intervention Assignment	Number of arms	Masking type	Allocation type	Study Phase
True	Treatment	Parallel	2	Double-blind	Randomized-controlled	N/A

Outcomes

Primary Outcomes:

PT-BR

Esperado: Diferença média de qualidade (ecointensidade) do músculo quadríceps, avaliada por ultrassom muscular, de ao menos 15% pré e pós-intervenção; diferença média de tamanho (espessura) do músculo quadríceps, avaliada por ultrassom muscular, de ao menos 8% pré e pós-intervenção.

EN

Expected: Mean change in muscle quality (echogenicity), assessed by muscle ultrasound, based on a minimal variation of 15% in pre and post intervention; mean change in size (thickness), assessed by muscle ultrasound, based on a minimal variation of 8% in pre and post intervention.

PT-BR

Observado: Diferença média de qualidade (ecointensidade) do músculo quadríceps, avaliada por ultrassom muscular, de 32% pré e pós-intervenção; diferença média de tamanho (espessura) do músculo quadríceps, avaliada por ultrassom muscular, de 15% pré e pós-intervenção.

EN

Observed: mean change in muscle quality (echogenicity), assessed by muscle ultrasound, of 32% in pre and post intervention; mean change in size (thickness), assessed by muscle ultrasound, based on a minimal variation of 15% in pre and post intervention.

Secondary Outcomes:

PT-BR

Esperado: menor redução dos níveis serviços de IGF-I no grupo intervenção (15%) comparado ao grupo controle (30%).

EN

Expected: smaller decrease on circulating levels of IGF-I at intervention group (15%) compared to control group (30%).

PT-BR

Observado: Menor redução dos níveis serviços de IGF-I no grupo intervenção (18%) comparado ao grupo controle (45%).

EN

Observed: Smaller decrease on circulating levels of IGF-I at intervention group (18%) compared to control group (45%).

Contacts

Contacts for Public Queries

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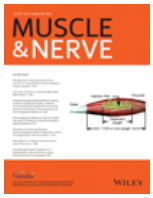
Anexo C – Normas de publicação do periódico, Qualis na área Interdisciplinar e comprovante de submissão do manuscrito referente ao Estudo 1, "*Reliability of skeletal muscle ultrasound in critically ill trauma patients*"

Muscle & Nerve



Edited By: Lawrence H. Phillips II, MD

Impact Factor: 2.713

ISI Journal Citation Reports © Ranking: 2015: 73/192 (Clinical Neurology); 128/256 (Neurosciences)

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AUTHOR GUIDELINES

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Research Articles	(150 words) Structured headings: Introduction, Methods, Results, Discussion	less than 10 is preferred	5 key words below the abstract page pertaining to all major points of the contribution	6000 words	Present original clinical and laboratory research and related topics.
Short Reports	(150 words) Structured headings: Introduction, Methods, Results, Discussion	Only 1 figure or table	5 key words below the abstract page pertaining to all major points of the contribution	1000 words	Provide preliminary communications of new data or research methods.
Invited Review Articles	(150 words) Does not need to be structured unless requested by Editor	less than 10 is preferred	5 key words below the abstract page pertaining to all major points of the contribution	Generally less than 6000 words. Exceptions after approval by the Editor	Describe current topics of importance and are usually solicited by the Editor.
Editorials	None	Generally no figures or tables	5 key words below the abstract page pertaining to all major points of the contribution	no more than 2000 words, with up to 12 references	Either free-standing brief commentary or discussion of an article published in the same issue of the Journal. Solicited by the Editor.
Case of the Month	(150 words) Structured headings: Introduction,	1 table and up to 4 figures.	5 key words below the abstract page pertaining	2,000 to 3,000 words	Presentation of rare or illustrative studies of

	Methods, Results, Discussion		to all major points of the contribution		noteworthy neuromuscular disorders
Noteworthy Cases **Letter to the Editor and Replies**	None	1 figure or table	5 key words below the abstract page pertaining to all major points of the contribution	500 words	Noteworthy Cases: Submitted in the form of a Letter to the Editor Letters: Comment on papers published in this journal or other relevant matters. Subtitles should not be used, and any acknowledgments should be included in the body of the letter.
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STYLE

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• Double Space entire manuscript, including reference section
• Organize manuscript in the following order, with each component beginning on a separate page and with a running title and page number in the upper right hand corner of each page

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Article Title (80 spaces Maximum)
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Acknowledgments if applicable (grant support and individuals who were of direct help in preparation of the study
Name/address and email address of the author to whom reprint requests are to be sent
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o **Abstract (page 2)**

Include title of article
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o **Text (starts on page 3)**

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o **Abbreviations**. All abbreviations used in the text should be listed and defined in alphabetical order on a separate page. This list should appear just before the references

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Listed and numbered in the order of citation and number them accordingly.
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Include the date of publication
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Separate pages
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Vertically oriented and no more than 6 inches wide
If table must exceed 1 typewritten page, duplicate headings on the second sheet
Numbered in the order in which they are cited in the text
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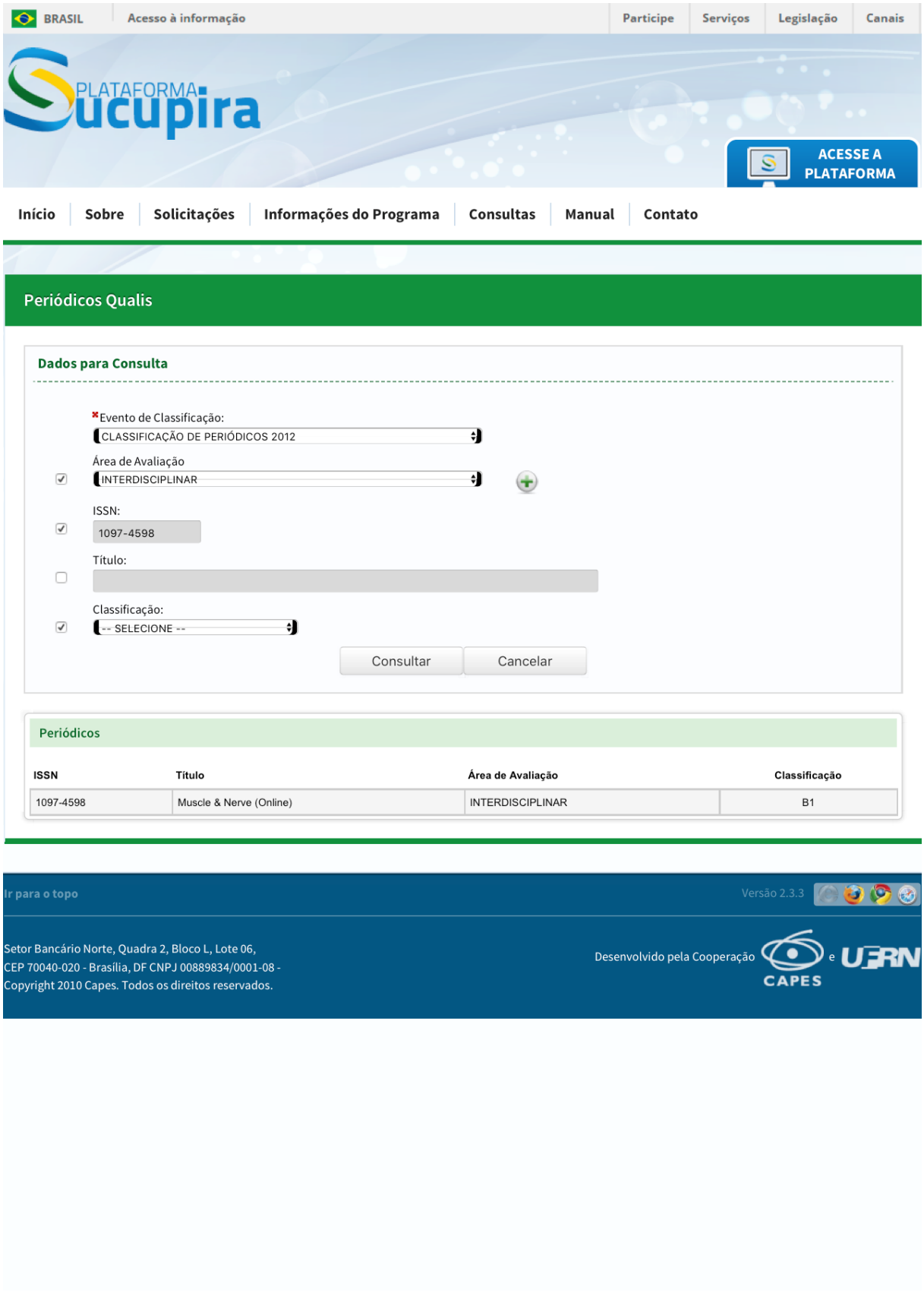
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Submission Confirmation

Thank you for your submission

Submitted to	Muscle and Nerve
Manuscript ID	MUS-16-0681
Title	RELIABILITY OF SKELETAL MUSCLE ULTRASOUND IN CRITICALLY ILL TRAUMA PATIENTS
Authors	Vieira, Luciana Mathur, Sunita Santana, Larissa Melo, Priscilla Maldaner, Vinicius Silva, Paulo Durigan, João Luiz Cipriano Jr, Gerson
Date Submitted	27-Aug-2016

**Anexo D – Normas de publicação do periódico, Qualis na área Interdisciplinar e comprovante de submissão do manuscrito referente ao Estudo 2, "*Acute skeletal muscle wasting assessed with ultrasound and mediators of muscle*

Critical Care

Impact Factor 4.950

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- Submission Guidelines

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- Fees and funding
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***growth and systemic inflammation in critically ill trauma patients: a prospective observational study*”**

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The following format for the 'Availability of data and materials section of your manuscript should be used:

"The dataset(s) supporting the conclusions of this article is(are) available in the [repository name] repository, [unique persistent identifier and hyperlink to dataset(s) in http:// format]."

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BioMed Central endorses the Force 11 Data Citation Principles and requires that all publicly available datasets be fully referenced in the reference list with an accession number or unique identifier such as a DOI.

For databases, this section should state the web/ftp address at which the database is available and any restrictions to its use by non-academics.

For software, this section should include:

- Project name: e.g. My bioinformatics project
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- Archived version: DOI or unique identifier of archived software or code in repository (e.g. enodo)
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- Programming language: e.g. Java
- Other requirements: e.g. Java 1.3.1 or higher, Tomcat 4.0 or higher
- License: e.g. GNU GPL, FreeBSD etc.
- Any restrictions to use by non-academics: e.g. licence needed

Information on available repositories for other types of scientific data, including clinical data, can be found in our editorial policies.

References

See our editorial policies for author guidance on good citation practice.

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission. For further information including example references please read our reference preparation guidelines.

What should be cited?

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited.

Unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE.

Any in press articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

How to format your references

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely; if the references are not in the correct style, they may need to be retyped and carefully proofread.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Authors may wish to make use of reference management software to ensure that reference lists are correctly formatted.

Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of

Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

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- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.
- Individual figure files should not exceed 10 MB. If a suitable format is chosen, this file size is adequate for extremely high quality figures.
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- Microsoft Word (suitable for diagrams and/or images, figures must be a single page)
- PowerPoint (suitable for diagrams and/or images, figures must be a single page)
- TIFF (suitable for images)
- JPEG (suitable for photographic images, less suitable for graphical images)
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- BMP (suitable for images)
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- Vector figures should if possible be submitted as PDF files, which are usually more compact than EPS files.
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- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.
- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.
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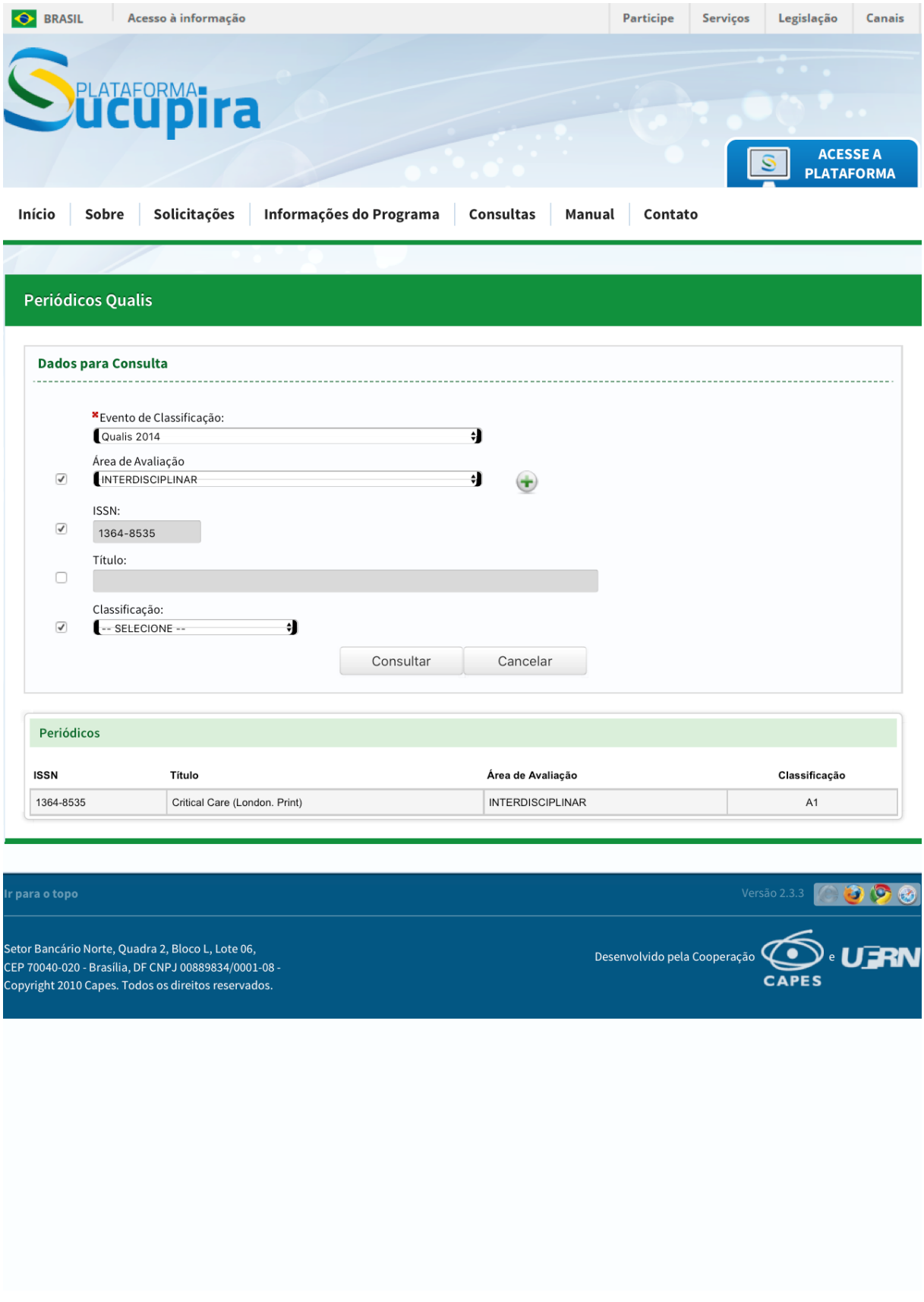
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Acute skeletal muscle wasting assessed with ultrasound and mediators of muscle growth and systemic inflammation in critically ill trauma patients: a prospective observational study
Luciana Vieira, MSc, PT; Priscilla Melo, MSc; Vinicius Maldaner, PhD; Joao Luiz Durigan, PhD; Carla Nunes Araujo, PhD; Vinicius Carolino Souza, MSc; Gaspar Chiappa, PhD; Sunita Mathur, PhD; Chris Burtin, PhD; Gerson Cipriano Jr, PhD
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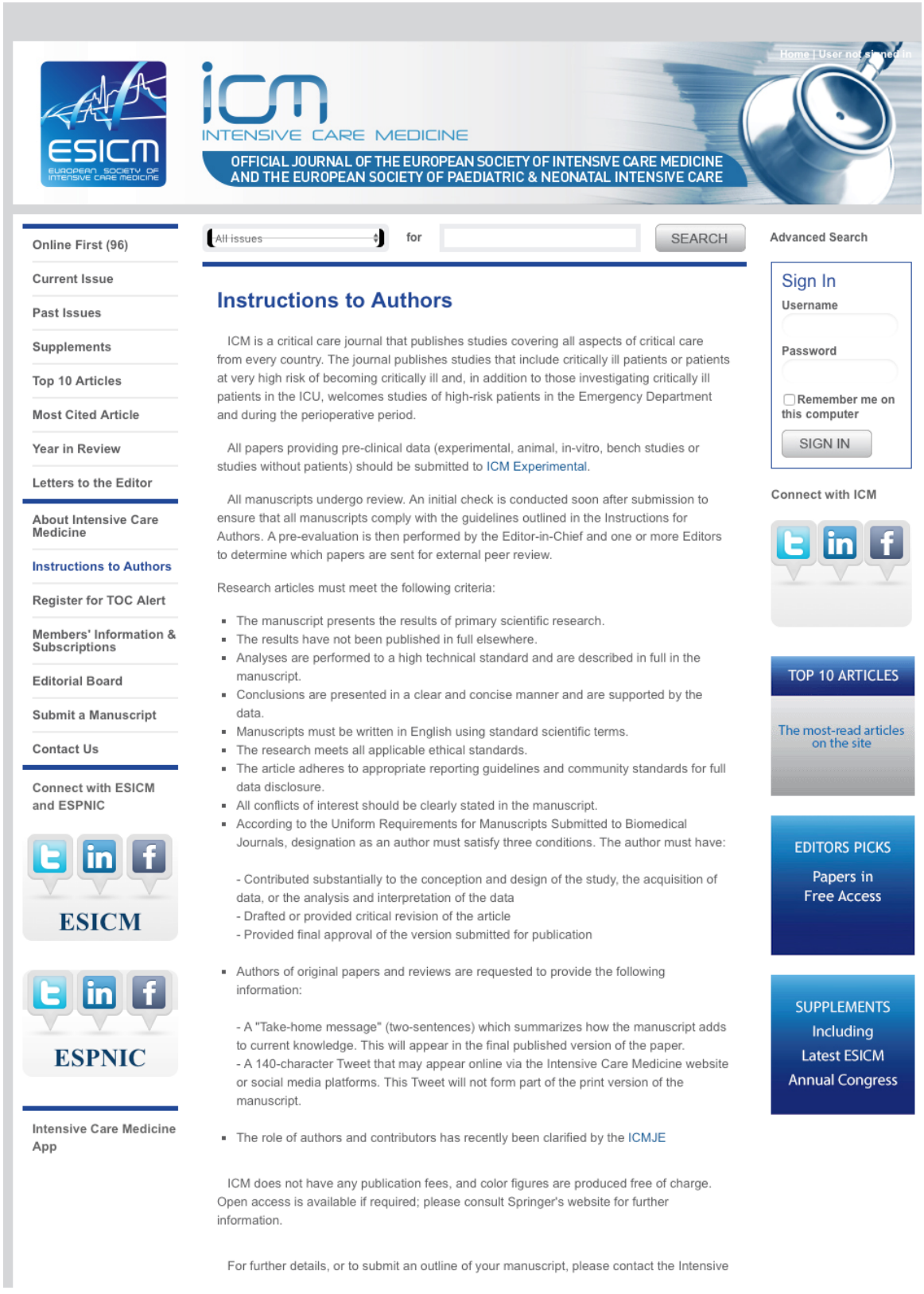
Anexo E – Normas de publicação do periódico, Qualis na área Interdisciplinar e comprovante de submissão do manuscrito referente ao Estudo 3, "*Neuromuscular electrical stimulation alleviates muscle wasting in critically ill trauma patients: a randomized controlled trial*"



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53. Brown KL, MacLaren G, Marino BS (2013) Looking beyond survival rates: neurological outcomes after extracorporeal life support. Intensive Care Med 39:1870-1872.

If you use Zotero, the ICM styling template can be found here.

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- Original papers must not exceed 3,000 words and should include no more than 5 illustrations or tables.
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- If authors consider that their manuscript needs to be longer than 3,000 words or contain more figures or tables, the reasons for this should be justified in the cover letter to the Editor-in-Chief.
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- Submission under the Images section must be of high scientific quality and value as well as providing didactic and self-explanatory lessons. They must be unique and adhere to ethical standards with patient/relative approval when appropriate, protection of patient identity and privacy, and local ethics approval as appropriate.
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- From the inside includes poetry, trivia, personal stories, thoughts and memories, sounding boards, obituaries or other qualitative materials that authors wish to share with colleagues.

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LaTeX macro package

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Please use no more than three levels of displayed headings.

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Abbreviations should be defined at first mention and used consistently thereafter.

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1. Negotiation research spans many disciplines [3].
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The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

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Combination Art

- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

Color Art

- Color art is free of charge for online publication.
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

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- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

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- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc."

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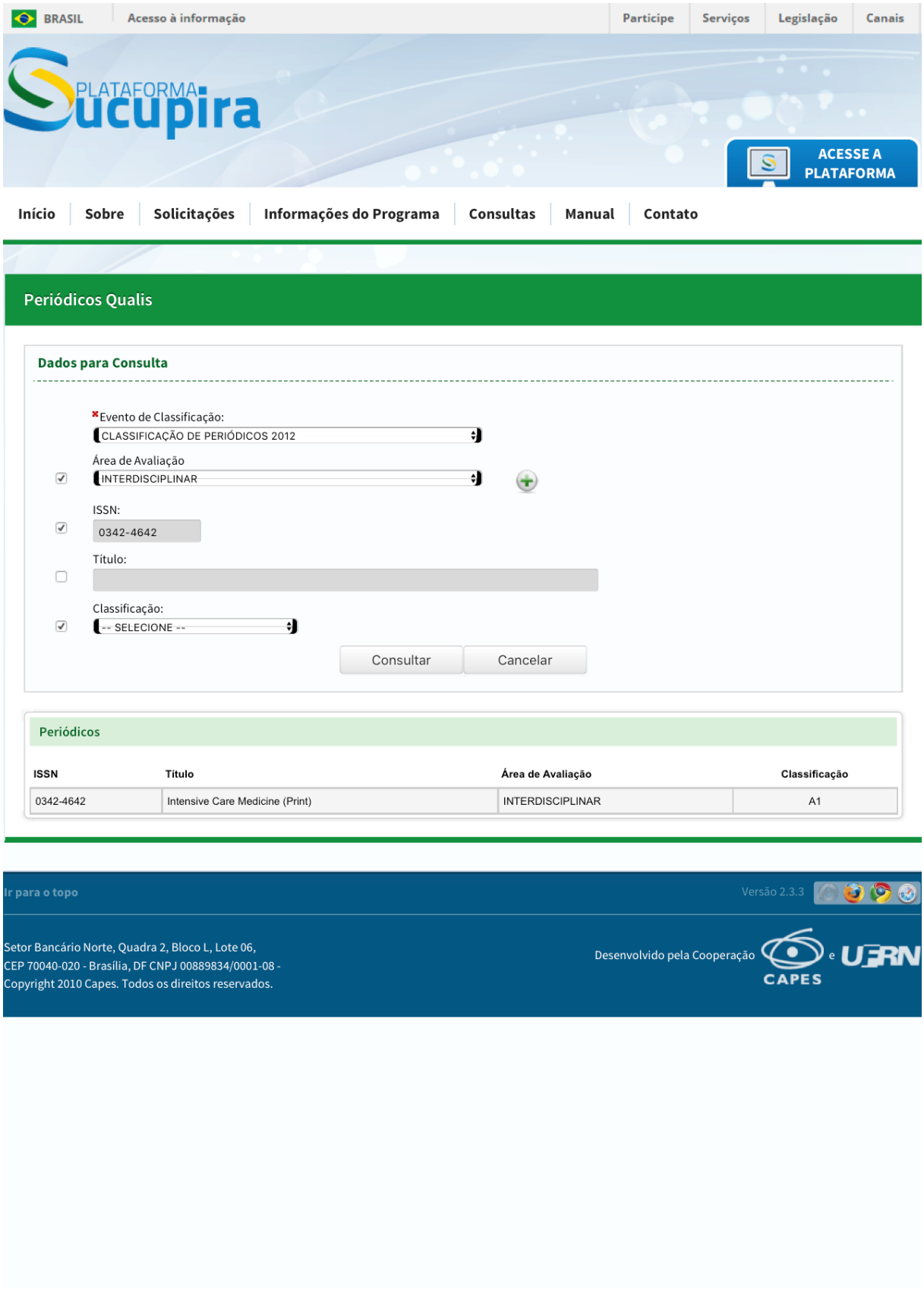
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